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# SPONTANEOUS MYOHEMOGLOBINURIA IN MAN

## Description of a Case with Recurrent Attacks

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SPONTANEOUS myohemoglobinuria is a disease characterized by the appearance of myohemoglobin in the urine combined with evidences of muscular dysfunction and without precipitating trauma or toxic agent of apparent importance. Other myohemoglobinurias in man are those resulting from crush injuries and those associated with the ingestion of poisoned eels or fish, called Haff disease. Eight cases of spontaneous myohemoglobinuria have been reported in the literature, the first by Meyer-Betz [1] in 1910. The published cases were summarized by the English workers Bywaters and Dibble [2] in 1943, who added 1 case of their own; 2 of these cases were in the French literature and the rest in the German literature. Only in Günther's case [3] (1924) was the diagnosis confirmed by the necessary spectrographic studies. Since the clinical and laboratory findings in certain hemoglobinurias and in porphyrinuria may simulate those of myohemoglobinuria, the other cases remain equivocal. Louw and Nielsen [4] reported a case in the Scandinavian literature in 1944 in which the diagnosis was well confirmed. The patient was a 13 year old boy who had had attacks of this disease since the age of 9. The family history revealed that in five generations there had been 8 instances of progressive muscular dystrophy transmitted as a sex-linked recessive. The authors suggested

From the Division of Medicine and the Spectrographic Laboratory, University of California Medical School.

1. Meyer-Betz, F.: Beobachtungen an einem eigenartigen mit Muskellähmungen verbundenen Fall von Hämoglobinurie, Deutsches Arch. f. klin. Med. **101**:85-127 (Nov.) 1910.

2. Bywaters, E. G. L., and Dibble, J. H.: Acute Paralytic Myohemoglobinuria in Man, J. Path. & Bact. **55**:7-15 (Jan.) 1943.

3. Günther, H.: Kasuistische Mitteilung über Myositis Myoglobinuria, Virchows Arch. f. path. Anat. **251**:141-149 (July) 1924.

4. Louw, A., and Nielsen, H. E.: Paroxysmal Paralytic Hemoglobinuria, Acta med. Scandinav. **117**:424-436, 1944.

that progressive muscular dystrophy and paralytic or spontaneous myohemoglobinuria may be related, the former being a chronic, low grade form, while the latter is an acute manifestation of the same process.

The patients ranged in age from 3 to 54 years, 5 being male and 3 female. The onset of the illness was usually sudden and sometimes accompanied with fever, nausea and vomiting. The muscles may be generally involved, or only isolated ones may be affected. There are pain, spasm and weakness, sometimes amounting to paralysis, and occasionally swelling of the afflicted muscles. The urine then becomes dark and may be nearly black, and it gives a positive reaction to the benzidine or guaiac test for occult blood. It contains albumin, creatine and yellowish pigmented casts. The disease varies in severity; the patient may die, apparently of uremia, or may recover and have many attacks. The three reported postmortem studies showed the striped muscles to be blanched, with variable degrees of degeneration, a loss of staining ability and deposition of a brownish pigment, probably myohemoglobin, in the renal tubules.

TABLE 1.—*Spectroscopic Absorption Bands*

| | Maximum | Minimum | Maximum | Minimum | Maximum |
|---|---|---|---|---|---|
| Oxyhemoglobin | 577 | 560 | 540 | 500 | 414 |
| Oxymyohemoglobin | 582 | 564 | 542 | 500 | 418 |

Cases of frank myohemoglobinuria are rare; minor degrees of it are probably more common. The present paper reports on a confirmed case, including clinical and laboratory studies. Since myohemoglobin has only recently been studied, a statement of its known properties and functions is of aid in understanding its pathologic physiology. The work of Millikan [5] in 1939 and that of Theorell [6] in 1934 furnish sound information on these points.

Myohemoglobin is a protein in the muscle sarcoplasm. It constitutes about one quarter of the total hemoglobin, and in general its properties are similar to those of blood hemoglobin. Both are combinations of protoporphyrin with iron and a specific globulin. Hemoglobin has a molecular weight of 68,000 and has four iron atoms per molecule, while myohemoglobin weighs 17,500 and contains only one iron atom. Its absorption spectrum is displaced about 4 millimicrons to the red from the principal bands of blood hemoglobin. Table 1 compares the principal absorption bands of oxymyohemoglobin and oxyhemoglobin, the data being taken from Theorell [6] and Heilmeyer.[7]

5. Millikan, G. A.: Muscle Hemoglobin, Physiol. Rev. **19**:503-523 (Oct.) 1939.

6. Theorell, H.: Kristallinisches Myoglobin: Die absolute Lichtabsorption von Oxy-, Carboxy-, Meta- und reduziertem Myoglobin, Biochem. Ztschr. **268**: 55-63, 1934.

7. Heilmeyer, L.: Spectrophotometry in Medicine, London, Adam Hilger, Ltd., 1943.

If oxymyohemoglobin and oxyhemoglobin are changed to the carbon monoxide forms, there occurs a displacement of their principal absorption bands to the blue; myohemoglobin shifts a maximum of 3 millimicrons and hemoglobin from 4 to 6 millimicrons.

The differences in weight of blood and muscle hemoglobin probably account for their considerable differences in renal threshold values. Hemoglobin, as has been shown by Gilligan and Blumgart [8] and Monke and Yuile,[9] averages 100 mg. per hundred cubic centimeters of plasma, while Yuile and Clark [10] have shown myohemoglobin to have a renal threshold of about 20 mg. per hundred cubic centimeters of plasma. It is possible to separate the two by ultracentrifugation and ultrafiltration; Bywaters and others [11] observed that a 9 millimicron collodin filter would permit passage of myohemoglobin and not of hemoglobin.

The chief function of myohemoglobin is as a respiratory pigment. It possesses a hyperbolic disassociation curve instead of the sigmoid curve of blood hemoglobin. Its affinity for oxygen is greater than that of blood hemoglobin and less than that of the oxidases. This property allows it to take oxygen from the blood and pass it to the cells. Furthermore, its rate of reaction with oxygen is extremely rapid, being of the order of a thousandth of a second. Citing Hill's work, Millikan [5] compared its affinity for oxygen to that of hemoglobin by showing that with a venous oxygen partial pressure of 40 mm. hemoglobin is 66 per cent saturated while myohemoglobin is 94 per cent saturated. After carefully considering these and other properties, Millikan concluded that myohemoglobin acts as a short time store for oxygen, tiding the muscle over from one contraction to the next.

With these facts in mind, a consideration of some related myohemoglobinurias gives a clearer understanding of spontaneous myohemoglobinuria in man. Equine paralytic myohemoglobinuria, a disease apparently identical in fundamental respects with spontaneous myohemoglobinuria in man, appears suddenly in an afflicted horse following resumption of work after a few days' rest. The horse staggers and becomes feverish, and the muscles swell and become hard and stiff. Shortly thereafter the animal passes red urine containing myohemoglobin and pigmented casts. It may recover, usually with a residual weakness,

8. Gilligan, D. R., and Blumgart, H. L.: March Hemoglobinuria: Studies of Clinical Characteristics, Blood Metabolism, with Observations on Three New Cases and Review of the Literature, Medicine **20**:341-395 (Sept.) 1941.

9. Monke, J. V., and Yuile, C. L.: Renal Clearanace of Hemoglobin in Dog, J. Exper. Med. **72**:149-165 (Aug.) 1940.

10. Yuile, C. L., and Clark, W. F.: Myohemoglobinuria: Study of Renal Clearance of Myohemoglobin in Dogs, ibid. **74**:187-196 (Sept.) 1941.

11. Bywaters, E. G. L.; Delory, G. E.; Rimington, C., and Smiles, J.: Myohaemoglobin in Urine of Air Raid Casualties with Crushing Injury, Biochem. J. **35**:1164-1168 (Nov.) 1941.

or may die from anuria due to blocking of the renal tubules by the muscle pigment. The disease is well described by Carlström [12] and Hutyra, Marek and Manninger.[13] Grzycki [14] stated that during an attack the animal's blood glucose, lactic acid, inorganic phosphate, creatinine and nonprotein nitrogen contents are raised while the carbon dioxide–combining power of the blood is decreased. Carlström's explanation is that there is an unduly rapid breakdown of glycogen from glycogen-rich muscles, with a resulting high production of lactic acid and direct muscular damage with release of myohemoglobin.

Stoeltzner,[15] Eichholtz,[16] Kaiserling [17] and Assmann and others [18] have described a peculiar malady called Haff disease, named after the locale in Germany, in which attacks of myohemoglobinuria in man followed ingestion of eels or fish poisoned by the discharge of the waste products of neighboring cellulose factories. The specific cause was found to be two acids in the resinous waste products, specifically pimaric and abietic.

A third type of myohemoglobinuria was studied by Bywaters and others,[11] being seen in some persons injured in an air raid who had been crushed beneath fallen masonry for several hours. These patients, with the restoration of circulating blood volume, passed smokey red urine which was rather acid and contained brownish casts. The urine gave a positive reaction to benzidine, and examination revealed it to have a spectrum corresponding to that of oxymyohemoglobin. The patients either recovered with a diuresis or anuria and progressive azotemia developed. Postmortem study showed areas of blanching and necrosis of the muscle together with a loss of staining ability. The kidneys had a tubular degeneration, with the deposition of brownish material which also gave a positive reaction to benzidine. The post-

12. Carlström, B.: Ueber die Aetiologie und Pathogenese der Kreuzlähme des Pferdes (Haemoglobinaemia paralytica), Skandinav. Arch. f. Physiol. **61**:11-224 (March) 1931; abstracted, Vet. Rec. **15**:1346, 1935.

13. Hutyra, F.; Marek, J., and Manninger, R.: Special Pathology and Therapeutics of the Diseases of Domestic Animals, ed. 4, London, Baillière, Tindall & Cox, 1938, vol. 3, p. 133.

14. Grzycki, S.: On the Pathology and Treatment of Paralytic Hemoglobinuria in the Horse, Berl. tierärztl. Wchnschr. **50**:789-790, 1934.

15. Stoeltzner, W.: Untersuchungen über die Haffkrankheit, Deutsche med. Wchnschr. **58**:1929-1932 (Dec.) 1932.

16. Eichholtz, F.: Ursache der Haffkrankheit, Deutsche med. Wchnschr. **58**: 1932-1934 (Dec.) 1932.

17. Kaiserling: Die histologische Untersuchung haffkranker Katzen, Deutsche med. Wchnschr. **58**:1934-1935 (Dec.) 1932.

18. Assmann, H.; Bielenstein, H.; Habs, H., and Jeddeloh, B.: Beobachtungen und Untersuchungen bei der Haffkrankheit 1932, Deutsche med. Wchnschr. **59**: 122-126 (Jan.) 1933.

mortem observations are similar to those described for spontaneous myohemoglobinuria in man and equine paralytic myoglobinuria in horses.

## REPORT OF A CASE

A. D., a 39 year old white man, was admitted to the hospital for study. He stated that since childhood he had become easily fatigued and that occasionally, following slight strain, he would get cramps in the legs and weakness associated with the passage of dark urine. He could voluntarily produce such an attack by stooping or holding himself in a semicrouching position. On doing so, the anterior muscles of his thighs would become painfully contracted almost immediately and so weak that he could not stand after a half-minute. The painful spasm usually lasted one or two hours, but the pronounced weakness persisted for two weeks. He never had fever, nausea or any other general symptoms. Commencing an hour or so after the strain, his urine would darken, and this darkening would increase to a maximum around six to eight hours, generally clearing in ten hours. The urine on the next morning was always of normal color. The patient stated that after an attack he could not produce another until at least two weeks had elapsed. In recent years he had observed a slow decrease in the strength of his arms and legs and had taken a job as doorman in which little demand on his strength was made. Aside from this he had always felt well and had been accepted by the Army in 1942, although he was discharged after several months because of his ailment. Ten years before he had had a chancre and the Wassermann reaction of his blood had been positive; for this he had received rather irregular treatment for two years with arsenical and bismuth preparations.

Physical examination revealed a well nourished, intelligent man without any obvious abnormality except for weakness of the upper part of the arms and thighs together with slight wasting of the proximal limb muscles; in notable contrast were the large and strong muscles of his calves. The muscular abnormalities were sufficiently extensive to lead the visiting consultant in neurology to make a diagnosis of progressive muscular dystrophy. Routine tests of the blood and urine gave normal reactions. The reactions to the Kahn and Kolmer tests of the blood were positive, while in the cerebrospinal fluid the reactions to the Kahn and Kolmer tests, the colloidal gold curve, the protein content and the cell count were normal.

While he was in the hospital, an attack was provoked in the manner described by the patient and resulted in the production of dark urine, which was found to contain myohemoglobin. During this and three subsequent hospitalizations these observations were confirmed and extended. Additionally, he has been seen over a year and a half in the clinic. During this period he has had three spontaneous attacks similar to those described. The patient feels that his weakness has continued to progress slightly.

*Special Studies.*—1. Method of Producing an Attack: The patient assumed a position with his knees and back well flexed, in such a way as to throw a considerable strain on the extensors of the legs. He immediately began to complain of cramping pain in his thighs. In less than a minute he could no longer hold himself erect and fell to the floor. He was assisted into bed, and examination showed that the quadriceps muscles were firmly contracted and tender; they remained tender and were in spasm for nearly two hours. There was moderate spasm of the muscles of his calves. Elsewhere there were no muscular changes. There were no variations in the blood pressure, and there was no nausea, vomiting or fever. The extreme weakness disappeared within five minutes, so that the

patient was able to walk; however, some weakness persisted in the legs for several days. There was no noted swelling of the muscles. Three weeks or more had to elapse before another attack could be produced. Attempts made before this period delayed the production of the next attack.

2. Urinary Changes: The urine taken when the patient was resting was of normal yellow color and without abnormal constituents. One and a half hours after the precipitating muscular strain the urine appeared darker, and the specimens after three, six and eight hours were a dark brown mahogany color. The ten hour specimen was only slightly discolored, and that of the next morning was normal in color. Coincident with the change in color the urine became acid in $p_H$, and large quantities of yellowish pigmented casts, about 20 to the low power field, appeared in the centrifuged specimen. While the urine collected for twenty-four hours prior to the strain had contained less than 0.5 Gm. of albumin, the urine for the twenty-four hours after the strain contained 2.0 Gm. The specimens collected between three and ten hours after the attack gave strong reactions to the benzidine and guaiac tests for occult blood, although they contained no red cells. The urine collected for twenty-four hours prior to the strain contained 0.25 Gm. of creatine and 1.26 Gm. of creatinine, the latter being a slightly lower content than normal. Following the strain, the urine collected for twenty-four hours contained 0.94 Gm. of creatinine and 1.37 Gm. of creatine. This is a low creatinine and a high creatine content. These findings are similar to those observed in

TABLE 2.—*Chemical Studies on Urine*

| | Sodium | Potassium | Creatine | Creatinine | Albumin |
|---|---|---|---|---|---|
| Twenty-four hours prior to strain | 8.0 Gm. | 1.5 Gm. | 0.25 Gm. | 1.27 Gm. | 0.5 Gm. |
| Twenty-four hours after strain producing myohemoglobinuria ..... | ..... | 1.7 Gm. | 1.37 Mg. | 0.94 Gm. | 2.0 Gm. |

myopathies. The results were confirmed on two other occasions. There were no significant changes in potassium level. Table 2 shows the tabulated results.

The porphyrins were assayed by the method of Dobriner and Rhoads.[19] The twenty-four hour urinary output after the strain was 0.065 Gm. of coproporphyrin of type III, a figure entirely within normal limits; no uroporphyrin of type III was present.

3. Spectrophotometric Identification: Specimens of urine were collected at varying intervals preceding and following the strain, and their absorption spectrums were determined on a model 10s Coleman spectrophotometer and checked with the model D Beckmen spectrophotometer. Corresponding specimens of oxalated blood were taken, and spectrophotometric studies were carried out on the separated plasma. Figure 1 shows the absorption curves for the plasma and figure 2 those for the urine. Comparison with the absorption curves for the plasma of normal persons showed no significant differences. The slight oxyhemoglobin peaks were the result of unavoidable hemolysis in the handling of blood. There were no discernible myohemoglobin peaks.

With the patient resting, the urine had an absorption spectrum without any appreciable maximums or minimums, with a gradually increasing absorption from the longer to the shorter wave lengths. This is the spectrum of a normal urine. The specimens collected one-half hour after strain were essentially the

19. Dobriner, K., and Rhoads, C. P.: The Porphyrins in Health and Disease, Physiol. Rev. **20**:416-459 (July) 1940.

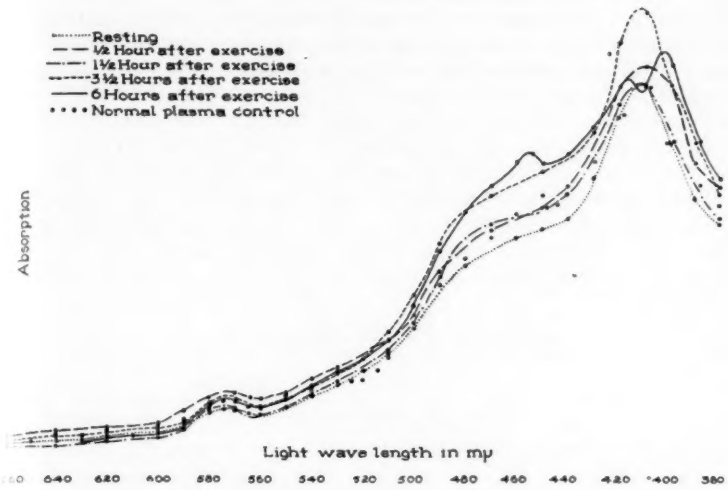
Resting
½ Hour after exercise
1½ Hour after exercise
3½ Hours after exercise
6 Hours after exercise
Normal plasma control
Absorption
Light wave length in mμ
660 640 620 600 580 560 540 520 500 480 460 440 420 400 380

Fig. 1.—Absorption spectrums of samples of plasma in a case of spontaneous myohemoglobinuria.

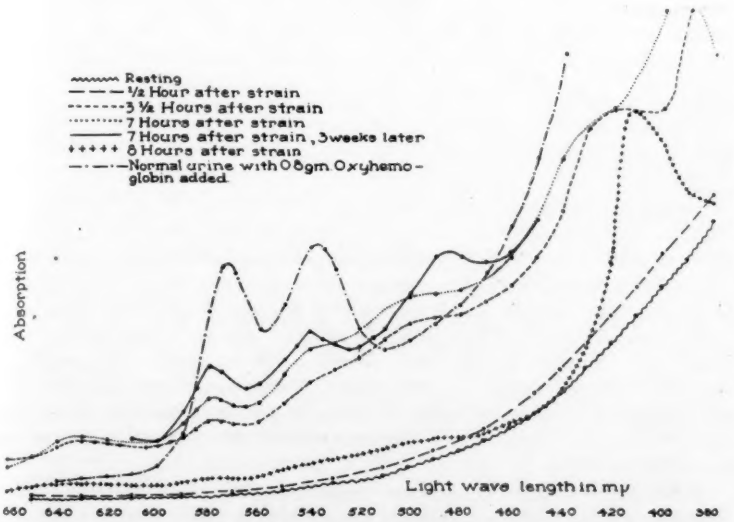
Resting
½ Hour after strain
3½ Hours after strain
7 Hours after strain
7 Hours after strain, 3 weeks later
8 Hours after strain
Normal urine with 0.8 gm. Oxyhemoglobin added.
Absorption
Light wave length in mμ
660 640 620 600 580 560 540 520 500 480 460 440 420 400 380

Fig. 2.—Absorption spectrums of samples of urine in a case of spontaneous myohemoglobinuria.

same. The three and a half hour and, to a greater extent, the seven hour specimens showed a well defined absorption band at 580 millimicrons, with a minimum of 565 millimicrons and a second maximum at 540 millimicrons. The substances responsible for the rising absorption from the region of 520 millimicrons toward the shorter wavelengths were not identified. The three and a half hour specimen showed a third maximum between 410 and 420 millimicrons. The eight hour voiding showed a return to nearly normal, with the exception of a strong peak at 417 millimicrons, perhaps representing metmyohemoglobin. Twenty-four hours after the strain the curve was entirely normal. The solid line curve in figure 2 represents a seven hour specimen taken three weeks later, which showed the principal oxymyohemoglobin bands even more clearly. Because of the background absorption, the absorption bands of myohemoglobin do not fall on the precise wave lengths of the purer

TABLE 3.—*Chemical Studies on Blood*

| | Before Strain | After Strain | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 1 Min. | 18 Min. | 2 Hr. | 2½ Hr. | 3½ Hr. | 5 Hr. | 6 Hr. | 24 Hr. |
| Protein, Gm./100 cc.* | 6.70 | .... | .... | ... | .... | .... | 6.50 | .... | 6.24 |
| | A/G = 4.25/2.45 | | | | | | A/G = 4.25/2.25 | | A/G = 4.00/2.24 |
| Carbon dioxide, Vol. % | 56.8 | .... | .... | ... | 52.7 | .... | 51.8 | .... | 57.6 |
| Chlorides, mg./100 cc. | 620 | .... | .... | ... | 650 | .... | 660 | .... | 653 |
| Urea, mg./100 cc. | 17 | .... | .... | ... | .... | .... | .... | .... | 18 |
| Nonprotein nitrogen, mg./100 cc. | 25 | .... | .... | ... | 26 | .... | 26 | .... | 25 |
| Creatine, mg./100 cc. | 0.75 | .... | .... | ... | .... | .... | 2.5 | .... | .... |
| Creatinine, mg./100 cc. | 1.00 | .... | .... | ... | .... | .... | 3.2 | .... | .... |
| Calcium, mg./100 cc. | 9.8 | .... | .... | ... | 9.8 | .... | 10.0 | .... | 10.0 |
| Sodium, mg./100 cc. | 315 | .... | .... | ... | .... | .... | 327 | 314 | 317 |
| Potassium, mg./100 cc. | 18 | .... | .... | ... | 17.0 | .... | 15.2 | 20.5 | 20.7 |
| Phosphorus, mg./100 cc. | 2.5 | .... | .... | ... | .... | .... | 2.5 | .... | 2.6 |
| Lactic acid, mg./100 cc. | 14.3 | 13.9 | 11.7 | 5.7 | .... | 9.23 | .... | 9.4 | 10.0 |
| Glucose, mg./100 cc. | 90 | .... | .... | 80 | .... | .... | .... | 95 | 90 |

* A signifies albumin; G, globulin.

solutions prepared by Theorell [6] but are displaced about 2 millimicrons to the blue. The dash-dot curve indicates the absorption of normal urine with added oxyhemoglobin and shows that the background shift is also true for oxyhemoglobin and, furthermore, that clear differentiation is possible between myohemoglobin and hemoglobin. Some of the specimens showed a 630 mu band, which would be expected if metmyohemoglobin were present. Saturation of the urine collected after strain with carbon monoxide displaced the principal absorption bands less than 3 millimicrons, compared with the 4 to 6 millimicrons which would be expected for oxyhemoglobin.

4. Blood Chemistry: The carbon dioxide–combining power and the sodium, potassium, chloride, lactic acid, calcium and phosphorus, serum protein, nonprotein nitrogen, urea, creatine and creatinine levels were studied. Table 3 summarizes the findings. The results of a glucose-insulin tolerance test were normal after the strain, as were those of the intravenous hippuric acid test. The plasma hemo-

globin content, determined by the method of Gilligan and others,[20] ranged from 5 to 15 mg. per hundred cubic centimeters, which is within the normal range. Serum taken at the height of the attack had, as determined by the method of Peters,[21] a creatinine content of 3.2 mg. per hundred cubic centimeters, a value nearly three times the upper limit of normal, according to Tierney and Peters,[22] and a creatine content of 2.5 mg. per hundred cubic centimeters, which is greatly in excess of the normal limit of 0.52 mg. set by the aforementioned authors. The results in the remainder of the tests of blood chemistry were within normal limits.

5. Other Tests: Fragility of the blood cells commenced with a 0.45 per cent concentration of sodium chloride and was complete in a 0.35 per cent solution. The Donath-Landsteiner test for a syphilitic autohemolysin gave negative reactions, as did actual chilling trials on the patient. Electrocardiographic records made before and after the myohemoglobinuria were normal. Retrograde and intravenous pyelography and other renal tests showed good function. Myohemoglobin appeared simultaneously in the urines collected through ureteral catheters during an attack.

## DIAGNOSIS

The diagnosis of myohemoglobinuria should be considered if dark urine yielding a positive reaction for occult blood in the absence of red cells is observed in a patient in whom there is no evidence of a hemolytic disease. A level of approximately 40 mg. of hemoglobin per hundred cubic centimeters of plasma (which is well below the renal threshold of 100 mg. per hundred cubic centimeters) must be reached to give an appreciable reddish tinge to the plasma. This is a higher concentration than would be expected of myohemoglobin, with its renal threshold of 20 mg. per hundred cubic centimeters. Therefore, presumptive exclusion of the diagnosis of hemoglobinuria can be made if inspection of samples of plasma taken just prior to the appearance of dark urine does not reaveal a strong reddish tinge. The association of albumin and many yellowish pigmented casts, especially if it occurs only during the acute episode, is further presumptive evidence. A positive diagnosis can be made only by identification of the characteristic absorption bands of myohemoglobin in the urine. Ultracentrifugation and ultrafiltration are of additional aid in making the differentiation from blood hemoglobin.

Clinically, the condition which might most closely simulate myohemoglobinuria is acute porphyria, of which Waldenström[23] has described a form associated with muscular wasting similar to progressive muscular

20. Gilligan, D. R.; Altschule, M. D., and Kalersky, E. M.: Studies of Hemoglobinemia and Hemoglobinuria Produced in Man by Intravenous Injection of Hemoglobin Solution, J. Clin. Investigation **20**:177-187 (March) 1941.

21. Peters, J. H.: Determination of Creatinine and Creatine in Blood and Urine with Photoelectric Calorimeter, J. Biol. Chem. **146**:179-186 (Nov.) 1942.

22. Tierney, N. A., and Peters, J.: Mode of Excretion of Creatine and Creatine Metabolism in Thyroid Disease, J. Clin. Investigation **22**:595-602 (July) 1943.

23. Waldenström, J.: Neurological Symptoms Caused by So-Called Acute Porphyria, Acta psychiat. et neurol. **14**:375-379, 1939.

dystrophy. Even without the wasting, the combination of muscular weakness, pain in the extremities and dark urine so often seen in acute porphyria is confusing enough. Fortunately, simple laboratory tests give adequate differentiation. None of the porphyrins give a positive reaction to the benzidine or guaiac test for occult blood, nor does porphobilinogen. Myohemoglobin will not give a positive reaction to tests for porphyrinuria, nor will it give a positive reaction to Watson's [24] test for urinary porphobilinogen, which test usually elicits a positive reaction in acute porphyria.

The differentation between certain hemoglobinurias and myohemoglobinuria is more readily made clinically than by laboratory tests. March hemoglobinuria is usually seen in healthy young males and consists in the appearance of dark urine containing hemoglobin, preceded by a gradual rise in plasma hemoglobin occasioned by severe exercise. As reported to date, it has been found uniformly that the exercise must be done with the patient in the erect or lordotic posture and never in a kyphotic position. The criteria of its benignity, its occurrence following severe exercise and the appearance of appreciable amounts of serum oxyhemoglobin distinguish it easily from myohemoglobinuria.

Syphilitic paroxysmal hemoglobinuria is usually precipitated by chilling, and often there is a positive Donath-Landsteiner reaction, indicating autohemolysin. Favism as a cause of paroxysmal hemoglobinuria offers no special problem in differential diagnosis. Paroxysmal nocturnal hemoglobinuria associated with chronic hemolytic anemia may be distinguished by its characteristic anemia, with thick red cells having an abnormal fragility.

## COMMENT

The results of the studies of blood chemistry in this patient are not such as to lend any support to the theory that myohemoglobinuria is caused by rapid glycolysis or glycogen-rich muscles. Certainly there was no rise in lactic acid, inorganic phosphate or blood glucose contents or decrease in the carbon dioxide–combining power, such as were reported in equine paralytic myohemoglobinuria.[25] The unchanged chloride contents, carbon dioxide–combining power and sodium level indicate little change in the acid-base balance of the blood. Furthermore, if rapid glycolysis were the cause, one might be able to precipitate an attack by injecting dextrose and insulin followed by epinephrine. This was attempted in our patient, and no myohemoglobinuria resulted.

It would be of great interest to clarify some possible relation existing between spontaneous myohemoglobinuria and other diseases having

24. Watson, C. J., and Schwartz, S.: A Simple Test for Urinary Porphobilinogen, Proc. Soc. Exper. Biol. & Med. **47**:393-394 (June) 1941.

25. Carlström.[12] Hutyra, Marek and Manninger.[13] Grzycki.[14]

some similar characteristics. The porphyrin excreted in large amounts during acute porphyria is uroporphyrin of type III, which differs from the protoporphyrin of myohemoglobin in the substitution of proponyl for vinyl groups; however, these two porphyrins belong to the same isomeric system, and, theoretically, it is possible to change protoporphyrin into uroporphyrin of type III. This suggests a possible link, that of defective muscular function, between the two diseases. Extensive studies have failed to show the mechanism involved in the production of march hemoglobinuria, no abnormalities of the blood, spleen or kidneys having been implicated. It is generally assumed that the pigment involved is blood hemoglobin; however, because of the need for the most careful spectrophotometric study to distinguish it from muscle hemoglobin, it is possible that this concept is in error and that the pigment may be a type of myohemoglobin. There exists a definite possibility that certain of the primary myopathies, such as progressive muscular dystrophy, are closely related to myohemoglobinuria and may be essentially the same disease, the latter being a series of acute manifestations and the former being a continuous process. In support of this hypothesis are the similarity of muscular involvement and creatine output and the occurrence of progressive muscular dystrophy in 8 members of a family with spontaneous myohemoglobinuria described by Louw and Nielsen.[4]

SUMMARY

The literature concerning myohemoglobinuria in man is reviewed. A new case of spontaneous myohemoglobinuria, with muscular weakness and wasting similar to that in progressive muscular dystrophy, is described, the diagnosis being confirmed by spectrophotometric studies. Other studies of the blood and urine are reported.

# NEUROCIRCULATORY ASTHENIA, ANXIETY NEUROSIS OR THE EFFORT SYNDROME

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THE PURPOSE of this paper is to summarize some of the conclusions and data from a comprehensive study of patients with neurocirculatory asthenia, anxiety neurosis or the effort syndrome.[1] These studies were conducted over a five year period [1a] (1942 to 1947), for the most part on service personnel. It is intended that this summary should be of use to those who are now handling or studying problems associated with this disorder. Although most of the important investigations on the subject have been made during and immediately after wars,[2] the problem of neurocirculatory asthenia is important in civilian

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1. Much of the work reported here was done under a contract, recommended by the Committee on Medical Research, between the Office of Research and Development and the Massachusetts General Hospital and has been reported elsewhere in detail. The members of this project who took part in some or all of the studies were: Responsible Investigators: Dr. Paul D. White, Dr. Stanley Cobb, Director: Dr. Mandel E. Cohen, Dr. Robert E. Johnson, Captain Ashton Graybiel, U. S. N. R., Dr. William P. Chapman, Dr. Daniel W. Badal, Dr. Carl Seltzer, Jane R. Brown, Frank Consolazio, Lt. Louis J. Pecora, U. S. N. R., Mary P. Lennon, Audrey Y. Dennison and Frances Cooperstein. Others who worked on other aspects of the problem included Dr. William D. Bridges, Dr. Elwyn Evans, Dr. Edwin O. Wheeler, and Eleaner W. Reed. Other work was done and is continuing under the auspices of the Medical Research and Development Board, Office of the Surgeon General, Department of the Army.

1a. Cohen, M. E.; Johnson, R. E.; Chapman, W. P.; Badal, D. W.; Cobb, S., and White, P. D.: A Study of Neurocirculatory Asthenia, Anxiety Neurosis, Effort Syndrome: Final Report to the Committee on Medical Research, Office of Scientific Research and Development, 1946.

2. (*a*) Da Costa, J. M.: On Irritable Heart: A Clinical Study of a Form of Functional Cardiac Disorder and Its Consequences, Am. J. M. Sc. **61:17**, 1871. (*b*) Lewis, T.: Reports upon Soldiers Returned as Cases of "Disordered Action of the Heart (D.A.H.)" or "Valvular Disease of the Heart (V.D.H.)," Medi-

life. In this paper we shall emphasize the data from our studies and the conclusions of the authors and shall not attempt to summarize the abundant literature on neurocirculatory asthenia; nor will we attempt to present in detail all the studies of the project, as they are being reported in separate papers by the various workers.

In this study 144 patients, all men, were investigated thoroughly. Ninety-six per cent were from service hospitals. The average age was 26.9 years. The symptoms were multiple, with cardiovascular, respiratory, nervous and muscular symptoms predominating. This type of disorder has been variously named neurocirculatory asthenia, anxiety neurosis, effort syndrome, Da Costa's syndrome, irritable heart, disordered action of the heart, soldier's heart, vasomotor instability, vasomotor neurosis, cardiac neurosis, neurasthenia, psychoneurosis, somatization reaction general, somatization reaction psychogenic cardiovascular reaction, somatization reaction psychogenic asthenic reaction, shell shock and combat fatigue. The exact limits of any of these terms have never been clearly defined. They all refer to a type of disorder in which several of the following features are striking: nervousness, easy fatigue, shortness of breath, palpitation, spells of faintness, giddiness or apprehensiveness, poor performance in muscular work and emotional stress. However, there is an absence of any diagnosable disease of the heart, lung, nervous system or thyroid to explain these symptoms.

For purposes of comparison with the 144 patients, 105 healthy soldiers, 25 soldiers convalescent from infected war wounds and 23 soldiers convalescent from infectious hepatitis were studied.

## CLINICAL PICTURE

Symptoms were multiple and of high incidence; those most outstanding were difficulties related to cardiovascular-respiratory function, to limitation of muscular activity and to emotional instability. At least twenty-four important symptoms occurred in 70 per cent of the cases (table 1). This is an amplification and confirmation of the description given by other authors.[2]

Abnormal physical findings were few. Such positive findings as there were occurred in a high percentage of cases and included high resting pulse rate, respiratory rate over 20, flushed face and neck, hyperactive knee jerks and ankle jerks and tremor of the fingers. These signs are not particularly helpful in differential diagnosis.

The results of all the routine clinical laboratory tests performed were within normal limits.[1a] These included hematologic studies, urinalysis, serologic test for syphilis and undulant fever, roentgen examination of the chest, gastrointestinal tract, teeth and sinuses, electrocardio-

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cal Research Committee (National Health Insurance), London, His Majesty's Stationery Office, 1917. (*c*) Wood, P.: Da Costa's Syndrome or Effort Syndrome, Brit. M. J. **1**:767, 805 and 845, 1941.

graphic and electroencephalographic tests and test of the basal metabolic rate. Chemical studies on samples collected when the patients were resting gave results which were within normal limits. For blood, these included determinations of the sugar, calcium, phosphate, nonprotein nitrogen, sodium, potassium, cholesterol and chloride contents, car-

TABLE 1.—*Prevalence of Symptoms in Patients with Neurocirculatory Asthenia Compared with That in Controls*

| | Percentage Incidence | | | |
|---|---|---|---|---|
| | Patients | | Controls | |
| Symptoms | With Chronic Disease | With Acute Disease | Convalescent from Infected Wounds | Healthy |
| Number of subjects | 74 | 25 | 25 | 55 |
| Symptoms significantly related to effort | 100 | 79 | 0 | 11 |
| Breathlessness | 99 | 79 | 24 | 13 |
| Palpitation | 93 | 82 | 20 | 15 |
| Tires easily | 91 | 93 | 44 | 7 |
| Irritability | 91 | 64 | .. | .. |
| Nervousness | 88 | 82 | 36 | 11 |
| Dizziness | 86 | 57 | 24 | 9 |
| Shakiness | 85 | 69 | 40 | 13 |
| Insomnia | 84 | 68 | 36 | 20 |
| No heavy work | 83 | 55 | .. | 0 |
| Faintness | 82 | 42 | 20 | 11 |
| Weakness | 81 | 63 | 28 | 2 |
| Apprehensiveness | 79 | 56 | 8 | 2 |
| Easily upset | 78 | 63 | .. | 7 |
| Vascular throbbing | 78 | 68 | 12 | 7 |
| Thoracic pain (left side) | 77 | 61 | 0 | 5 |
| Sweating | 76 | 73 | 20 | 24 |
| Trembling | 74 | 64 | 36 | 15 |
| Inability to get a satisfactory breath | 74 | 41 | 16 | 2 |
| Unhappiness | 73 | 59 | 20 | 15 |
| Flushes | 73 | 58 | 20 | 11 |
| Loss of weight | 72 | 72 | 52 | 20 |
| Headache | 71 | 46 | 8 | 33 |
| Attacks | 70 | 72 | 12 | 2 |
| Prolonged pain in the left side of the chest | 65 | 42 | 0 | 4 |
| Nightmares | 63 | 55 | 60 | 16 |
| Panting | 62 | 52 | 4 | 5 |
| Fear of death (in attacks) | 62 | 52 | 0 | 5 |
| Sighing | 61 | 39 | 12 | 9 |
| "Gas" | 59 | 31 | 4 | 24 |
| Anorexia | 55 | 59 | 28 | 20 |
| Nervous chill | 54 | 46 | 24 | 7 |
| Smothering | 50 | 28 | 8 | 5 |
| Paresthesia | 49 | 36 | 12 | 4 |
| Vomiting or diarrhea | 45 | 43 | 0 | 7 |
| Attacks, no obvious stimulus | 46 | 61 | 4 | 2 |
| Attacks, apparently precipitated | 43 | 32 | 8 | 0 |
| Dry mouth | 42 | 33 | 8 | 15 |
| Urinary frequency | 42 | 23 | 12 | 7 |
| Syncope | 41 | 29 | 24 | 13 |
| Always tired | 32 | 22 | 4 | 5 |
| No light work | 10 | 28 | .. | 0 |
| Symptoms, exclusively after effort | 7 | 0 | .. | 0 |

bon dioxide-combining power, carbon dioxide content and pressure $p_H$, oxygen content, oxygen saturation and carbonic anhydrase; for urine they included determinations of ketosteroids, thiamine, riboflavin, $N^1$-methylnicotinamide and ascorbic acid.

On grounds of history alone two groups of patients were differentiated.[3] Those who had a life course of symptoms of neurocirculatory

3. Cohen, M. E.: Bull. Cardiovascular Diseases, p. 7, National Research Committee, Division of Medical Sciences acting for the Committee on Medical Research of the Office of Scientific Research and Development, 1944.

asthenia or those who could never do hard work or athletics were designated as having "chronic neurocirculatory asthenia." Those who gave convincing evidence of good health, ability to do muscular work or athletics and nervous stability previous to the onset of illness were designated as having "acute neurocirculatory asthenia." Although this classification was based in every instance on history alone, nevertheless in all the quantitative studies mentioned in the following paragraphs which yielded significant differences between healthy controls and patients with neurocirculatory asthenia, mean values for those with the acute form of the disease fall between those for the healthy controls and those for the patients with the chronic form of the disease.

### STUDIES OF MUSCULAR WORK

Patients and controls were studied during and after muscular work.[4] Moderate work consisted of walking on a treadmill,[5] and hard work consisted of running on a treadmill,[5] stepping up and down on a 20 inch (50.8 cm.) step[6] and stepping up and down with a pack on the back.[7]

Table 2 shows that in the basal condition the pulse and respiratory rates are slightly abnormal in neurocirculatory asthenia. However, there was no difference between patients with neurocirculatory asthenia and controls in regard to oxygen consumption and the blood lactate concentration while resting.

Although differences at rest were not great, during muscular work striking abnormalities appeared. One might ask what the characteristics are of a man in good condition for muscular work.[8] Important features are (1) his ability to take up a high amount of oxygen rapidly, (2) his ability to do a given amount of work with less displacement of his physiologic mechanisms than the average and (3) his ability

4. Cohen, M. E.; Johnson, R. E.; Cobb, S.; Chapman, W. P., and White, P. D.: Studies of Work and Discomfort in Patients with Neurocirculatory Asthenia, J. Clin. Investigation **23**:934, 1944.

5. (*a*) Robinson, S.: Experimental Studies of Physical Fitness in Relation to Age, Arbeitsphysiol. **10**:251, 1938. (*b*) Johnson, R. E.; Brouha, L., and Darling, R. C.: A Test of Physical Fitness for Strenuous Exertion, Rev. canad. de biol. **1**:491, 1942.

6. Brouha, L.; Graybiel, A., and Heath, C. W.: The Step Test: Simple Method of Measuring Physical Fitness for Hard Muscular Work in Adult Man, Rev. canad. de biol. **2**:86, 1943.

7. A "Pack" Test of Physical Fitness for Hard Muscular Exercise, Report no. 1, Office of Scientific Research and Development, Boston, Harvard Fatigue Laboratory, April 13, 1942. Darling, R. C.; Johnson, R. E.; Pitts, G. C.; Consolazio, F. C., and Robinson, P. F.: Effects of Variations in Dietary Protein on the Physical Well Being of Men Doing Manual Work, J. Nutrition **28**:273, 1944.

8. Robinson, S.; Edwards, H. T., and Dill, D. B.: New Records in Human Power, Science **85**:409, 1937. Data recalculated.

TABLE 2.—*Subjects with Neurocirculatory Asthenia Compared with Controls (Basal Values, Values After Moderate Work and Values After "Exhausting" Work)**

| | Patients with Neurocirculatory Asthenia | | | | | | Healthy Controls | |
|---|---|---|---|---|---|---|---|---|
| | Total | | Chronic | | Acute | | | |
| | No. | Value | No. | Value | No. | Value | No. | Value |
| **Resting** | | | | | | | | |
| Pulse rate | 49 | 79 | .. | .... | .. | .... | 55 | 71 |
| Respiratory rate | 50 | 15.8 | .. | .... | .. | .... | 34 | 13.2 |
| Basal metabolic rate | 50 | + 4 | .. | .... | .. | .... | 34 | + 1 |
| Ventilation—liters per square meter per minute | 50 | 4.53 | .. | .... | .. | .... | 34 | 4.77 |
| Blood lactate—mg./100 cc. | 50 | 12.6 | 32 | 11.8 | 18 | 13.9 | 23 | 16.2 |
| **Moderate Exercise** | | | | | | | | |
| **Walking at 3.5 miles per hour at 8.9 per cent grade** | | | | | | | | |
| Maximum pulse rate | 25 | 161 | .. | .... | .. | .... | 20 | 150 |
| Ventilation—cc./kilogram per minute | 20 | 657 | .. | .... | .. | .... | 20 | 574 |
| Oxygen consumption—cc./kilogram per minute | 20 | 28.6 | .. | .... | .. | .... | 20 | 28.8 |
| Ventilatory efficiency | 20 | 4.46 | .. | .... | .. | .... | 20 | 5.08 |
| Blood lactate—mg./100 cc. | 61 | 41.1 | 42 | 44.6 | 19 | 33.6 | 41 | 21.0 |
| Blood sugar—mg./100 cc. | 22 | 111 | .. | .... | .. | .... | 18 | 107 |
| **"Exhausting" Exercise** | | | | | | | | |
| **Step test—20 inch step (30 steps per minute) Maximum Effort** | | | | | | | | |
| Duration | 94 | 109 | 71 | 100 | 23 | 136 | 40 | 190 |
| Sum of three recovery pulse rates | 94 | 369 | 71 | 369 | 23 | 371 | 40 | 356 |
| "Index of fitness" | 94 | 30 | 71 | 28 | 23 | 36 | 40 | 59 |
| **Running 7.0 miles per hour at 8.9 per cent grade Maximum Effort** | | | | | | | | |
| Duration | 69 | 92 | 55 | 84 | 14 | 125 | 60 | 202 |
| Sum of three recovery pulse rates | 60 | 420 | 46 | 418 | 14 | 424 | 35 | 408 |
| "Index of fitness" | 60 | 22 | 46 | 19 | 14 | 31 | 35 | 50 |
| Lactate 5 minutes after—mg./100 cc. of blood | 68 | 94 | 50 | 93 | 18 | 100 | 46 | 118 |
| Ventilation—cc./kilogram per minute | 19 | 1,082 | .. | .. | .. | ... | 20 | 1,299 |
| Oxygen consumption—cc./kilogram per minute | 18 | 39.5 | .. | .. | .. | ... | 20 | 46.9 |
| Ventilatory efficiency | 18 | 4.35 | .. | .. | .. | ... | 20 | 5.44 |
| **For the same duration** | | | | | | | | |
| Ventilation—cc./kilogram per minute during | | | | | | | | |
| 0 to 1 | 20 | 829 | .. | .. | .. | ... | 20 | 645 |
| 1 to 2 | 20 | 1,037 | .. | .. | .. | ... | 20 | 977 |
| 2 to 3 | 20 | 1,108 | .. | .. | .. | ... | 20 | 1,216 |
| Oxygen consumption—cc./kilogram per minute during | | | | | | | | |
| 0 to 1 | 18 | 33.8 | .. | .. | .. | ... | 20 | 35.0 |
| 1 to 2 | 13 | 40.0 | .. | .. | .. | ... | 20 | 43.9 |
| 2 to 3 | 7 | 37.7 | .. | .. | .. | ... | 19 | 46.5 |
| Ventilatory efficiency during | | | | | | | | |
| 0 to 1 | 18 | 4.29 | .. | .. | .. | ... | 20 | 5.42 |
| 1 to 2 | 13 | 3.38 | .. | .. | .. | ... | 20 | 4.59 |
| 2 to 3 | 8 | 3.46 | .. | .. | .. | ... | 19 | 3.92 |
| Lactate—mg./cc. per second of test time | 68 | 1.31 | 50 | 1.48 | 18 | 0.85 | 46 | 0.46 |

* Basal refers to supine, resting and fasting states; moderate work refers to the treadmill walk—3.5 miles per hour at 8.9 per cent grade, and "exhausting" work refers to the treadmill run—7.0 miles per hour at 8.9 per cent grade. The run is for a maximum of 5 minutes or until the patient's stopping point. Ventilatory efficiency = oxygen consumption ÷ pulmonary ventilation. "Index of fitness" = duration of hard work test ÷ sum of three recovery pulse rates.

to achieve and tolerate as a result of maximal work a great displacement of physiologic mechanism.

Patients with neurocirculatory asthenia showed poor ability to take up oxygen (fig. 1) during hard work and a large displacement for a moderate amount of work (table 2), and they never accomplished maximal work giving great displacement. In other words, they were diametrically opposite to the man in good condition for muscular work.[4]

In order to compare physiologic responses during work in patients with neurocirculatory asthenia and in controls, a task was chosen which could be finished by both. A treadmill walk was used for this purpose. After moderate exercise of fixed duration and amount, patients with neurocirculatory asthenia showed higher pulse rates and higher blood lactate concentrations (table 2) than controls.[9] Pulmonary ven-

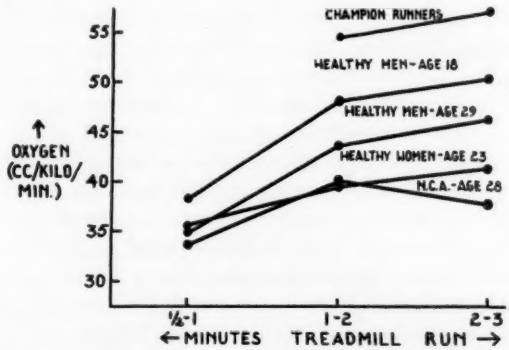


Fig. 1.—Oxygen consumption during hard work. All subjects ran at seven miles per hour up a grade of 8.9 per cent for the time shown in the abscissa. Ordinates show average oxygen consumption in cc. per kilogram of body weight per minute for 4 champion distance runners (9), 77 healthy men aged 18 years (12), 20 healthy men aged 29 years (13), 17 healthy women aged 23 years (14) and 20 patients with neurocirculatory asthenia aged 28 (10). The figure shows throughout that the poor work groups, the older men, the women and the patients have the lowest consumption.

tilation was higher in the patients and oxygen consumption was the same in the two groups, giving lower ventilatory efficiency in the former while they were walking.

In hard work tests, patients did not last as long as did control subjects. The subjects were instructed to go for a full five minutes or for as long as they could. The average duration for patients with the chronic form of the disease on a treadmill run was eighty-four seconds and for those with the acute form of the disease it was one hundred and twenty-five seconds, as compared with two hundred and two

9. Cohen, M. E.; Consolazio, F. C., and Johnson, R. E.: Blood Lactate Response During Moderate Exercise in Neurocirculatory Asthenia, Anxiety Neurosis or Effort Syndrome, J. Clin. Investigation **26**:339, 1947.

seconds for control subjects. Similar results were obtained in the step test. For patients with chronic neurocirculatory asthenia the stopping point was reached in one hundred seconds, for those with the acute form it was reached in one hundred and thirty-six seconds and for the controls it was reached in one hundred and ninety seconds.

It will be noted that the sum of three recovery pulse rates is slightly higher for the patients than for the control subjects despite the fact that the duration of the run performed by the former was much shorter. The "index of fitness," [5b] calculated by dividing the duration of the run by the sum of the three recovery pulse rates, is therefore low in neurocirculatory asthenia. The maximum lactate concentration after hard work is not as high. This is misleading, since the patient probably does not perform long enough to raise the blood lactate level. When the time of performance is considered, however, it can be seen (table 2) that as calculated in amount of lactate per cubic centimeter of blood per second of running time the lactate concentration in neurocirculatory asthenia is more than double that of the healthy subject, i. e., 1.31 as compared to 0.60 mg. The patient with chronic neurocirculatory asthenia has the greatest concentration of lactate per unit of time; the patient with the acute form of the disease is intermediate between the control subject and the patient who is chronically affected. Physiologic responses to maximum effort in hard work tests are not strictly comparable since the duration of maximal performance is not the same for each person. However, for the first two minutes of the run and in a few instances for the third minute it was possible to record measurements for patients with neurocirculatory asthenia who lasted for that time and to compare them with those for the healthy control subjects during the same interval. Striking differences were noted. During this run, oxygen consumption and ventilatory efficiency were lower in the patients than in the healthy controls. At first it may seem surprising that the patients used less oxygen during running,[10] as this might suggest high mechanical efficiency. Actually this is part of a general pattern, as can be seen from figure 1, since champion runners [8] use most oxygen, healthy men use less, young men [11] using more than older men,[12] women less than this [13] and finally patients with neuro-

10. Cohen, M. E.; Johnson, R. E.; Consolazio, F. C., and White, P. D.: Low Oxygen Consumption and Low Ventilatory Efficiency During Exhausting Work in Patients with Neurocirculatory Asthenia, Effort Syndrome, Anxiety Neurosis, J. Clin. Investigation **25**:292, 1946.

11. Heath, C. W., and others: What People Are: A Study of Normal Young Men, Cambridge, Mass., Harvard University Press, 1945. Heath, C. W.: Unpublished data.

12. Harvard Fatigue Laboratory: Unpublished data.

13. Metheny, E.; Brouha, L.; Johnson, R. E., and Forbes, W. H.: Some Physiologic Responses of Women and Men to Moderate and Strenuous Exercise: A Comparative Study, Am. J. Physiol. **137**:318, 1942.

circulatory asthenia [10] the least. This fact of low oxygen consumption during hard work together with high lactate concentration suggests abnormal aerobic metabolism and high anaerobic metabolism.

In general, when one compares groups of subjects who work hardest and longest on these tests with those who work least, i. e., women, men in poor training [14] and patients with neurocirculatory asthenia,[1] differences between the two groups become more apparent as the intensity and duration of the work tests are increased.

In other words, the more the work is stepped up the more clearly does the "poor work group" separate itself from the "good work group." When the subjects are at rest the measurable differences are few and small. During moderate exercise, measurable differences appear consistently. In groups whose performance during hard work tests, i. e., running, is of short duration walking is associated with high blood lactate concentration, high pulse rate, high pulmonary ventilation and low ventilatory efficiency. However, average oxygen consumption is the same for all groups during the walk.

During the portion of a hard work test which all subjects perform for a comparable length of time at a fixed pace and grade, all the differences seen in walking are accentuated. In addition, oxygen consumption is lowest in the groups who do not run well (fig. 1).

When subjects run at a fixed pace until they reach their stopping point, those who run longest have higher oxygen consumption, higher pulmonary ventilation, higher blood lactate levels, higher ventilatory efficiency and lower pulse.

In other words, during work of the same duration regardless of the intensity the "poor work group" showed the greatest physiologic displacements except for oxygen consumption. With regard to hard work, carried out to the point at which the subjects stopped running, the "good work groups" ran longest and reached the greatest levels of physiologic displacements. These observations may seem to be contradictory; they are not, however, if one realizes that the "good work group," as exemplified by outstanding athletes, perform longer and harder tasks while undergoing maximum physiologic displacements. During moderate work comparable to that done by other persons they show less physiologic change.

We concluded from this study that with either moderate or "exhausting" muscular work, during which patients and controls alike perform for the same duration and at the same rate, there are many measurable abnormalities in patients with neurocirculatory asthenia. All the findings in table 2 are consistent with the hypothesis that aerobic metabolism is abnormal in these patients. This is strikingly illustrated in

14. Knehr, C. A.; Dill, D. B., and Neufeld, W.: Training and Its Effects on Man at Rest and at Work, Am. J. Physiol. **136**:148, 1942.

figure 1, and the high blood lactate concentration demonstrates a reciprocal high oxygen debt.

It cannot be stated whether these findings apply specifically to patients with neurocirculatory asthenia or whether they are the general signs of poor health, chronic illness, poor runners or poor state of training.

English workers in 1943 concluded from studies of lactic acid levels in the effort syndrome [15] that the patients "showed . . . no major biochemical abnormality in their response. The $p_H$ and lactate were

TABLE 3.—*Incidence in Neurocirculatory Asthenia of Symptoms Involving Breathing* *

| Group Studied | Patients: With Chronic Disease | Patients: With Acute Disease | Controls: Convalescent | Controls: Healthy |
|---|---|---|---|---|
| Number of subjects | 74 | 25 | 25 | 55 |
| **From present illness** | | | | |
| 1. Breathlessness | 99 | 79 | 24 | 13 |
| 2. Inability to get a satisfactory breath | 74 | 41 | 16 | 2 |
| 3. Panting | 62 | 52 | 4 | 5 |
| 4. Sighing | 61 | 39 | 12 | 9 |
| 5. Gas mask trouble | 55 | 17 | 12 | 15 |
| 6. Smothering | 50 | 28 | 8 | 5 |
| **From past history** | | | | |
| 7. Trouble breathing in water (while swimming) | 75 | 22 | 12 | 10 |
| 8. Always short of breath | 41 | 0 | 8 | 7 |
| **During hard work test** | | | | |
| Number of subjects | .. 65 .. | | .. 31 .. | |
| 9. Breathlessness severe enough to cause patients to stop | .. 62 .. | | .. 18 .. | |

* Significance of differences in incidence of symptoms; patients with chronic disorder versus healthy controls—all differences significant; patients with chronic disorder versus those with acute disorder—all differences significant except for 3, 4 and 6; patients with chronic disorder versus convalescent controls—all differences significant; patients with acute disorder versus convalescent controls—all differences significant except 2, 5, 6 and 7; patients with acute disorder versus healthy control subjects—all differences significant except for 5 and 7, and convalescent control subjects versus healthy control subjects—significant difference shown only with regard to number 2.

in keeping with the amount of work done . . ." and, further, that the patients' difficulty was simply a matter of lack of "persistence." Our findings, reported in 1944,[4] of abnormally high blood lactate concentration evidencing abnormal oxygen debt made this conclusion untenable. Our later work provided further evidence of abnormal aerobic metabolism.[16] In work reported in 1946 the English workers revised their previous conclusions and found definite chemical abnormalities in neurocirculatory asthenia, and their finding of high oxygen consump-

15. Jones, M., and Scarisbrick, R.: Effort Intolerance in Soldiers: Review of Fve Hundred Cases, War Med. **2**:901 (Nov.) 1942.

16. Cohen and others.[1a] Cohen, Johnson, Consolazio and White.[10]

tion in the recovery period [17] is an important addition to our general concept as expressed here and elsewhere.[1a]

### STUDIES OF BREATHING AND DYSPNEA

Patients with neurocirculatory asthenia commonly complain of shortness of breath, inability to draw a satisfactory breath and inability to do hard work because of breathlessness. The incidence of symptoms involving breathing is given in table 3, which shows significant differences between patients and controls. The incidence is higher among patients with chronic illness than among those with the acute form and higher among convalescent controls than among healthy controls.

Quantitative studies of respiration showed that while resting and breathing oxygen patients with neurocirculatory asthenia have more rapid respiratory rates and more shallow breathing than do healthy control subjects.

The ventilation index [18]

$$\text{V. I.} = \frac{\text{Ventilation}}{\text{Vital capacity}} \times \left(1 + \frac{\text{ideal weight}}{\text{actual weight}}\right) \Big/ 2$$

was abnormally high in patients for all four speeds of exercise. This was due to a high ventilation factor and not to vital capacity, which was normal in our series of patients.[1a] (The mean vital capacity for 54 healthy men was 2,387 cc. per square meter of body surface and for 73 patients with neurocirculatory asthenia 2,362 cc.).

The ventilation index is usually an objective correlate of the subjective phenomenon of dyspnea. As shown in figure 2, when the level of ventilation index was the same, more of the patients than of the healthy controls complained of dyspnea. Furthermore, the degree of dyspnea complained of was greater in patients than in healthy controls doing the same amount of exercise and with the same ventilation index. Further details have been reported by Cohen and White.[18a]

### CARDIOVASCULAR STUDIES

Cardiovascular studies showed only a few significant deviations from the normal.

The pulse rate at rest, during exercise and after exercise was high, averaging 8 to 10 beats per minute higher than that in healthy controls.

17. Jones, M., and Mellersh, V.: A Comparison of the Exercise Responses in Anxiety States and Normal Controls, Psychosom. Med. **8**:180, 1946.

18. Harrison, T. R.; Turley, C. F.; Jones, E., and Calhoun, J. A.: Congestive Heart Failure: The Measurement of Ventilation as a Test of Cardiac Function, Arch. Int. Med. **48**:377 (Sept.) 1931.

18a. Cohen, M. E., and White, P. D.: Studies of Breathing, Pulmonary Ventilation and Subjective Awareness of Shortness of Breath (Dyspnea) in Neurocirculatory Asthenia, Effort Syndrome, Anxiety Neurosis, J. Clin. Investigation **24**:520, 1947.

In our series the size of the heart, as determined from measurements of the diameter and area of the heart in roentgenograms, was not significantly different in the two groups (50 subjects in each group). Our findings are described elsewhere [19] and do not confirm the conclusion of others [20] that neurocirculatory asthenia is characterized by the presence of a small heart. The electrocardiogram, made with the patient at rest and after mild exercise (Master's test), was within normal limits.[21]

Other normal findings were related to responses of the blood pressure and the pulse to changes of posture on a tilt table, resting venous pressure, blood volume, vital capacity, circulation time and resting cardiac output as measured by the acetylene method of Grollman and compared with normal standards.[22] Measurement of the cardiac output by the direct Fick method employing catheterization of the right

| DYSPNEA → | NONE | SLIGHT | MODERATE | SEVERE |
|---|---|---|---|---|
| CONTROLS | 63% | 28% | 8% | 1% |
| PATIENTS | 6% | 36% | 44% | 14% |

Fig. 2.—Dyspnea (at ventilation index of 15 to 25). The ventilation index of Harrison [18] is said to be an objective correlate of the subjective phenomenon of dyspnea. This shows that the incidence and severity of dyspnea in neurocirculatory asthenia are out of proportion to the ventilation index as well as to the severity of the exercise described previously.

auricle of the heart [23] gave mean values that were within the limits of those reported by Stead and his associates [24] for normal subjects with

19. Carlotti, J.; Cohen, M. E., and White, P. D.: The Heart Size in Neurocirculatory Asthenia, Effort Syndrome or Anxiety Neurosis, Am. Heart J. **34**: 552, 1947.

20. Master, A. M.: Neurocirculatory Asthenia Due to Small Heart, M. Clin. North America **28**:577, 1944.

21. White, P. D.; Cohen, M. E., and Chapman, W. P.: The Electrocardiogram in Neurocirculatory Asthenia, Anxiety Neurosis or Effort Syndrome, Am. Heart J. **34**:390, 1947.

22. Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C Thomas, Publisher, 1932. Burwell, C. S., and Strayhorn, W. D.: Concretio Cordis: Clinical Study, with Observations on Venous Pressure and Cardiac Output, Arch. Surg. **24**:106 (Jan.) 1932.

23. Cournand, A.: Measurement of the Cardiac Output in Man Using the Right Heart Catheterization, Federation Proc. **4**:207, 1945.

24. Stead, E. A., Jr.; Warren, J. V.; Merrill, A. J., and Brannon, E. S.: The Cardiac Output in Male Subjects as Measured by the Technique of Right Atrial Catheterization: Normal Values with Observations on the Effect of Anxiety and Tilting, J. Clin. Investigation **24**:326, 1945.

"evidence of anxiety." Our patients seemed tense and apprehensive during the procedure. Values obtained by the Grollman method were lower than those obtained by the direct Fick method.[18]

Ballistocardiographic studies were done on 30 patients. We were not able to satisfy ourselves as to the reliability or the theoretic soundness of this method in its present state of development as applied to the measurement of cardiac output in patients, and we are in agreement with Cournand, Hamilton, and others in their cautious evaluation of the method.[25]

One of the positive findings in patients with neurocirculatory asthenia was the structure of the capillaries of the finger nail folds described in a report by Cobb, Cohen and Badal.[26] Table 4, composed from that work, shows the result of visual examination of the nail fold with a capillary microscope. Control subjects for the most part had capil-

TABLE 4.—*Capillary Types in the Finger Nail Folds of Patients with Neurocirculatory Asthenia and of Controls* [26]

| Group of Subjects | Number of Subjects | Percentage Prevalence* | |
|---|---|---|---|
| | | Simple Loops | Complex Loops |
| Patients with neurocirculatory asthenia (chronic) | 32 | 44 | 56 |
| Patients with neurocirculatory asthenia (acute) | 16 | 47 | 53 |
| Controls (healthy) | 23 | 79 | 21 |
| Controls (osteomyelitis) | 21 | 65 | 35 |

* The difference in incidence of simple loops is statistically significant as between patients with neurocirculatory asthenia and healthy controls and between controls with osteomyelitis and healthy controls. The same is true for the incidence of complex loops.

laries of a simple U type (simple loops), whereas patients with neurocirculatory asthenia had predominantly crossed loop, twisted or dentate and crenate forms (complex loops). We do not know whether this difference represents an abnormality which could be demonstrated in fixed microscopic sections. The difference between the two types of controls, i. e., healthy men and men with infected wounds, suggests that these abnormalities are not restricted to patients with neurocirculatory asthenia but may occur in other conditions.

### STUDIES OF PAIN AND DISCOMFORT

Common among symptoms of neurocirculatory asthenia are pain in the chest, gastrointestinal pain, indigestion, headaches and excessive

25. Hamilton, W. F.: Notes on the Development of the Physiology of Cardiac Output, Federation Proc. **4**:183, 1945. Cournand.[23]

26. Cobb, S.; Cohen, M. E., and Badal, D. W.: Capillaries of the Nail Fold in Patients with Neurocirculatory Asthenia (Effort Syndrome, Anxiety Neurosis), Arch. Neurol. & Psychiat. **56**:643 (Dec.) 1946.

self observation, i. e., symptoms involving discomfort (table 1). Therefore an investigation was made of the patients' perception of painful stimuli and their reaction to an endurance of these.

Thermal stimuli consisted of a beam from a hot lamp in the Hardy-Wolff radiation apparatus shining for three seconds on the blackened forehead.[27] The level at which thermal stimulus was perceived as painful was not significantly different when patients and controls were tested. However the level at which the subject winced, i. e., reacted, was lower for patients than for 44 controls (0.364 Gm. calories per second per square centimeter). As the stimulus became stronger, some subjects pulled their heads aways from the apparatus. This occurred most frequently and at the lowest levels when patients with chronic neurocirculatory asthenia were being tested. This work has been reported in detail by Chapman, Cohen and Cobb [28] and the relation of the responses to the symptom "nervousness" pointed out.

The response to the discomfort of sustained hand gripping was tested by means of a hand dynamometer, the use of which has been described by others.[29] The patients' maximum grasp was determined in each hand by duplicate trials.[29a] The dynamometer was then set at 60 per cent of the subject's maximum grasp, and the subject was asked to hold it at this level as long as he could. There was no significant difference in maximum grip strength between patients with neurocirculatory asthenia and healthy controls. However, duration of gripping at 60 per cent of the maximum was significantly less for 58 patients with chronic neurocirculatory asthenia (thirty-six seconds) than for healthy controls (forty-eight seconds).

The patients' response to pain and discomfort corresponds well with the complaints which they make and which others make about them that stimuli and situations which involve discomfort or endurance are not handled well.[29a]

### PSYCHOLOGIC TESTS [30]

Psychologic tests [31] were administered in order to collect quantitative evidence bearing on three questions.

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27. Cohen, M. E., and White, P. D.: Progress Report, Committee on Medical Research, Office of Scientific Research and Development, July 1944. Cohen, Johnson, Cobb, Chapman and White.[4]

28. Chapman, W. P.; Cohen, M. E., and Cobb, S.: Measurements of Levels of Heat Stimulus Perceived as Painful and Producing Wince and Withdrawal Reactions in Patients with Neurocirculatory Asthenia, Anxiety Neurosis or Effort Syndrome and in Control Subjects, J. Clin. Investigation **25**:890, 1946.

29. Dunlap, J. W.: Tests of the "Ability to Take It," Report no. 11, Civil Aeronautics Administration, Division of Research, February 1943.

29a. Cohen and others.[1a] Cohen, Johnson, Cobb, Chapman and White.[4]

30. Tests were administered and analyzed for the most part by Jane R. Brown and Audrey Y. Dennison.

31. Cohen, and White.[27] Cohen and others.[1a]

1. Are patients with neurocirculatory asthenia normally intelligent? Scores in the Wechsler-Bellevue [32] tests (54 cases) were within average limits, the mean for the intelligence quotient being 107.2 for the verbal score and 103.2 for the performance score.

2. Was the patients' disability related to an unusual attitude toward war? Thurstone's "war attitude test" [33] was administered to 74 patients with neurocirculatory asthenia, 47 healthy soldiers, 25 convalescent wounded soldiers and 36 conscientious objectors. The scores of the patients and of the control soldiers were the same and placed them in the "neutral" category. In contrast, the scores of the conscientious

TABLE 5.—*Comparison of Patients with Neurocirculatory Asthenia and Controls in Three "Neurosis Tests"*

| Test and Component of Test | Patients | | Controls | |
|---|---|---|---|---|
| | With Chronic Disease | With Acute Disease | Convalescent | Healthy |
| I. Psychosomatic inventory (36) | | | | |
| Physiologic score | | | | |
| Mean percentage ratings..... | 7.6 | 15.2 | 41.7 | 58.8 |
| Normal scale | | | | |
| Psychologic score | | | | |
| Mean percentage ratings..... | 26.2 | 29.1 | 54.2 | 56.8 |
| Normal scale | | | | |
| Number of subjects..... | 72 | 34 | 23 | 56 |
| II. Personality inventory (37) | | | | |
| Mean score..... | 62 | 56 | .... | 32 |
| Neurotic category | | | | |
| Number of subjects..... | 72 | 29 | .... | 54 |
| III. Multiplex personality inventory (38) | | | | |
| Mean score | | | | |
| Hysteria..... | 75.6 | 67.1 | 55.8 | 47.1 |
| Depression..... | 74.0 | 71.7 | 56.5 | 48.6 |
| Hypochondriasis..... | 73.9 | 67.7 | 54.2 | 50.7 |
| Psychasthenia..... | 64.0 | 57.4 | 53.6 | 47.3 |
| Number of subjects..... | 61 | 29 | 24 | 55 |

objectors placed them in the "strongly pacifistic category." None of the soldiers had scores which placed them in the "militaristic" categories, which corresponded with a general impression of lack of "militaristic" feelings in the American Army.[1a]

3. Do psychologic tests whose scores do not depend on the observers' bias confirm the clinical impression that neurocirculatory asthenia properly belongs to the group called by others "neurosis"? Three questionnaire tests were administered, namely, the psychosomatic inventory,[34]

32. Wechsler, D.: The Measurement of Adult Intelligence, ed 2, Baltimore, Williams & Wilkins Company, 1941.

33. Thurston, L. L.: Attitude Toward War Scale, Chicago, University of Chicago Press, 1930.

34. McFarland, R. A., and Seitz, C. P.: A Psychosomatic Inventory, J. Applied Psychol. **22**:327, 1938.

the personality inventory [35] and the multiphasic personality inventory.[36] Table 5 shows that in each of the three tests patients with neurocirculatory asthenia obtain scores which place them in the neurosis category. In addition, patients with the acute form are less abnormal than those with the chronic form. Convalescent controls obtained scores which in all instances tended in the direction of the "neurosis scores," probably because some symptoms like those of "anxiety neurosis" are sometimes found (table 1) in normal convalescence.[37] However, this does not mean that normal convalescence and neurosis are identical.[38] The exact meanings of these tests are not clear.

In addition, 22 patients were given the thematic apperception test [38a] in order to test out the usefulness of a so-called projective test. Results of tests scored by three different observers did not give impressive agreement. This, taken with the fact that the test involved unproved assumptions, made its usefulness of doubtful value in our hands.

TABLE 6.—*Incidence of Neurocirculatory Asthenia in Relatives of Patients with Chronic Neurocirculatory Asthenia and of Healthy Control Subjects*

| | Patients (67 Families) | Healthy Controls (54 Families) |
|---|---|---|
| Fathers | 18.5% | 0% |
| Mothers | 58.0% | 0% |
| Brothers and sisters | 12.6% | 0% |
| Total number of relatives about whom satisfactory information was obtained | | |
| Fathers | 59% | 54% |
| Mothers | 58% | 54% |
| Brothers and sisters | 199% | 175% |

## FAMILIAL PREVALENCE OF NEUROCIRCULATORY ASTHENIA

A study was made of familial prevalence for two reasons: first, a high proportion of patients stated that symptoms similar to their own occurred in other members of the family; secondly, earlier writers have touched on the possibility that this disorder may be hereditary.[39]

35. Bernreuter, R. G.: Manual for the Personal Inventory, Stanford University, Calif., Stanford University Press, 1938.

36. McKinley, J. C., and Hathaway, S. R.: The Identification and Measurement of the Psychoneuroses in Medical Practice: The Minnesota Multiphasic Personality Inventory, J. A. M. A. **122**:161 (May 15) 1943.

37. Cohen, M. E., and White, P. D.: Progress Report, Committee on Medical Research, Office of Scientific Research and Development, December 1944. Cohen and others.[1a]

38. Brodman, K.; Mittelmann, B., and Wolff, H. G.: Psychologic Aspects of Convalescence, J. A. M. A. **129**:179 (Sept. 15) 1945.

38a. Murray, H. A.: Thematic Apperception Test, Cambridge, Mass., Harvard University Press, 1942.

39. Beard, G. M.: A Practical Treatise on Nervous Exhaustion (Neurasthenia): Its Symptoms, Nature, Sequences, Treatment, New York, William Wood & Co., 1880.

The prevalence of neurocirculatory asthenia was high in mothers, fathers and siblings of patients.[37] The differences shown in table 6 between relatives of healthy controls and those patients with neurocirculatory asthenia are statistically significant. Figure 3 illustrates the familial pattern in the families of 15 of these patients as contrasted with the families of 15 healthy control subjects.

Since interviews with our patients suggested a possible familial prevalence, direct examination of 15 relatives was made. Results of the examinations corroborated the diagnosis in every case. This validated in part the method of diagnosing the condition from the history of relatives whom we did not examine.

Data on the familial incidence of other disorders show that manic-depressive psychosis, schizophrenia, angina pectoris and epilepsy are

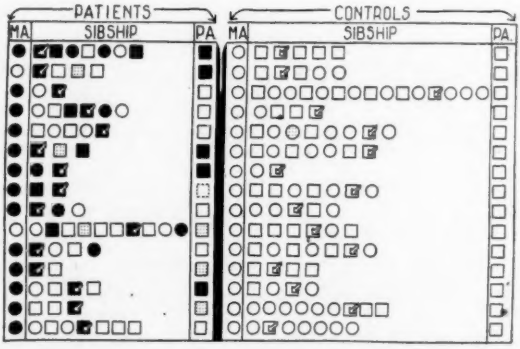


Fig. 3.—Familial incidence of neurocirculatory asthenia.[1a] This illustrates the familial pattern of the disorder in the families of patients as compared with the families of 15 healthy controls. The circle indicates females, the square males, the stippled square probable neurocirculatory asthenia, the black square neurocirculatory asthenia and the square with the arrow our patient or subject.

no more frequent among the close relatives of patients with neurocirculatory asthenia than they are among the close relatives of control subjects, which suggests that something more than the familial incidence of nonspecific neurologic, psychiatric or cardiologic disease is being dealt with.[1a]

In acute neurocirculatory asthenia there is but slight evidence of familial prevalence as compared with that in the chronic disorder.

The incidence of neurocirculatory asthenia in the 37 sons and daughters taken from a group of 50 parents diagnosed as having neurocirculatory asthenia twenty years ago was 48.6 per cent. This differed significantly from the incidence of the disorder of 5.6 per cent in 234 controls, the significance ratio being 5:1. This demonstrated that the incidence of neurocirculatory asthenia or anxiety neu-

rosis in the sons and daughters of patients with that disorder was significantly higher than in the general population.[40]

The data on familial prevalence was examined in the light of present day knowledge of human heredity.[41] When families with one affected parent are compared with those with two affected parents, the incidence in the offspring is 37 per cent and 62 per cent respectively. If the disorder is inherited, these figures suggest the possibility that the inheritance is that of the mendelian dominant. However, some of our data are inconsistent with this hypothesis, particularly the relatively higher incidence among mothers as compared with fathers. It is obvious that demonstration of familial prevalence does not necessarily imply that a disorder is hereditary. For instance, it might be contagious or related to other household factors.

### COURSE

In patients already ill with neurocirculatory asthenia, symptoms are seemingly provoked by a wide variety of stimuli ranging from effort and emotion-provoking situations to no obvious factor. This characteristic of the disorder has been emphasized by previous writers on the subject.[2a, b]

### ANATOMIC CHANGES

We have no information on the changes, gross or microscopic, observed at autopsy on subjects with neurocirculatory asthenia, nor are there any postmortem studies adequately described in the literature.[41a]

### CAUSE

The cause or causes of neurocirculatory asthenia are unknown. We have no crucial data in this study that reveal the cause, nor are there any convincing studies in the literature. However, certain points are evident. First, in the search for the cause of chronic neurocirculatory asthenia, factors other than the immediate ones must be considered. Secondly, there is a high familial prevalence of the disorder. This suggests that search should be made for household or hereditary factors. Finally, a clear differentiation has to be made between the problem of the cause and the problems of what makes symptoms worse or what provokes an exacerbation. This differentiation is not always clearly made in the loose thinking that is sometimes present in the fields of

40. Wheeler, E. O.; White, P. D.; Reed, E., and Cohen, M. E.: Familial Incidence of Neurocirculatory Asthenia ("Anxiety Neurosis," "Effort Syndrome"), J. Clin. Investigation, to be published.

41. Roberts, J. A. F.: An Introduction to Medical Genetics, London, Oxford University Press, 1940.

41a. Hartshome, H.: On Heart Disease in the Army, Am. J. M. Sc. 48: 89, 1864. Da Costa.[2a]

so-called psychodynamics and psychosomatic medicine. Finally, the measurable abnormalities in this disorder must be given due consideration in establishing the cause.

## COURSE AND BIOGRAPHIC EVENTS IN PATIENTS

This section will comprise a brief presentation of facts relating to the duration of the disorder, patients' answers to the question of what makes symptoms worse," factors associated with the onset or with exacerbation of the disease according to patients' histories, "emotional trauma" and "external physical" hardships during service. A follow-up of the course of the illness subsequent to our examination will also be discussed.

*Duration.*—The average age at the onset of the disease in 68 patients with the chronic form was twenty-one years, and the disease had lasted from three months to twenty-eight years, with a mean of seven years. Thirty-three patients with the acute form had an average age of 25 years, and the disease had lasted from two months to nine years, with a mean of 1.8 years. We should like to remind the reader of the somewhat unorthodox usage in this paper of the terms "chronic" and "acute" as applied to the disorder. Duration of symptoms is not the basis for these definitions but rather the period of good health and of ability to do work.

*What Makes Symptoms Worse?*—Patients' symptoms were made worse, according to their statements, by muscular work, by any strong emotion-provoking situation, by thinking about something unpleasant and often by no obvious stimulus. We observed only 5 patients of 76 with the chronic form of the disorder [1a] in whom muscular effort was the sole precipitant, and the same small percentage described an emotion-provoking situation as the sole precipitant of symptoms.

*Factors Associated with the Onset of Exacerbations as Judged From the Patients' Biographies.*—According to patients' stories, the onset of exacerbation of the disorder sometimes corresponds approximately in time with one or another of a wide variety of factors. In order of frequency of incidence these included family troubles, various types of infectious disease, overwork in service, father's cruelty, alcoholism or other misbehavior, death or illness in the family and many others.

This type of data is not particularly final in interpreting the course of the disease. First, we did not have collateral evidence in most cases as to the reliability of the patients' stories; secondly, the exact time relationship between biographic events and the course of disorder was not satisfactorily established and, thirdly, there is no necessary or automatic causal relationship between the events and the disorder even if they have close temporal relationship.

*Emotional Trauma and External Physical Hardship During Exercise.*—A tabulation was made of several sources of emotional trauma and of external physical hardships in military service. This was done to determine whether patients experienced more personal difficulties than did controls. No significant differences were found in the incidence of domestic problems between patients and healthy controls. Practically all patients (99 per cent of those with the chronic disorder and 85 per cent of those with the acute form) blamed the army for their difficulties and over 50 per cent believed, as did half of the convalescent wounded soldiers, that they were unfit for further service and that no treatment would help. A high percentage of patients with the acute form of the disorder and of convalescent controls reported a harrowing experience in combat. It is not clear to what extent these various differences reflected or influenced the symptoms or were reflections of particular attitudes of the patients.[1a]

*Follow-up Studies.*—Follow-up letters were sent to patients and to control subjects to find out what course the disorder had taken up to two years after examination. Of 39 patients, 85 per cent had been discharged from service. Three per cent reported that they were well, 85 per cent had symptoms off and on and in only 20 per cent was there unchanged. Twenty-six healthy control subjects were all still in service, and in none had neurocirculatory asthenia developed. This inadequate study demonstrated that discharge from military service does not automatically and immediately cure the disorder. These findings are in agreement with a larger follow-up study after World War I.[42]

From data collected in a twenty to twenty-five year follow-up [42a] of 55 patients, it was found that 15 per cent became completely well, 85 per cent had symptoms off and on and in only 20 per cent was there moderate or severe disability. These patients had been treated by "simple reassurance" for the most part.

Only 5 per cent of the men had significant disability. Of 177 patients in this study, 62 per cent were women and 38 per cent men, suggesting the distribution of the disorder between men and women in the civilian population.

Additional information on 166 of 173 patients in the study gives approximately the same follow-up results as above, which suggests a relatively benign course for this disorder and further that various therapeutic claims must be judged against knowledge of the course of the disorder over many years.

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42. Grant, R. T.: Observations on the After-Histories of Men Suffering from the Effort Syndrome, Heart **12**:121, 1945.

42a. Wheeler, E. O.; White, P. D.; Reed, E., and Cohen, M. E.: Follow-up and Familial Studies in Neurocirculatory Asthenia (Anxiety Neurosis, Effort Syndrome), Proc. New England Heart Assn., 1947-1948.

COMMENT

No attempt is made here to summarize the literature on neurocirculatory asthenia. In many instances our work corroborates or extends observations of other workers. Various periods in the development of the concept of the disorder can be summarized in the beliefs of some of the more important workers. Da Costa,[2a] in describing the disorder in patients in the Civil War, did not limit his description to cardiovascular-respiratory symptoms but included nervous and digestive symptoms as well in his classic description of "irritable heart." He emphasized fever, diarrhea, hard field service and marching as important in causing the disorder. Sir Thomas Lewis [2b] in World War I recognized that the disorder had existed in many of his patients before the war. He sought to avoid the "presumption" that there is a cardiac malady by use of the term "effort syndrome," referring to the occurrence without adequate provocation of "symptoms and signs that follow exercise" if no signs of disease are anywhere discovered. Wood [2c] in World War II emphasized the resemblance of the symptoms to fear and was impressed by the importance of environment and experience in causing the disorder.

Our particular emphasis has been on the physiologic abnormalities, on the high familial prevalence of the disorder and on the chronic and acute types. We have demonstrated that the disorder is not identical with the symptoms of either effort or fear.[1] We do not believe that environment and experiences have been demonstrated either by us or by others to be the major factors in causing the disorder.

We conclude that neurocirculatory asthenia actually exists and is not evidence of malingering or simply a mechanism aroused during the war for purposes of evading military service. The disorder is common in civilian as well as in military life. Among other factors, the various terms used to refer to it make difficult the problem of assessing its exact frequency.

With regard to the various terms used, we would state that no term is ideal. We do not propose a new term or set of terms, believing that new names should await discovery of the cause or causes of what is now known as neurocirculatory asthenia, effort syndrome or anxiety neurosis. It is particularly important that present terminology should not mislead the users of it. For instance, if the term "anxiety neurosis" is used, it is important to realize that whereas anxiousness is one symptom of this disorder there are many others and that whereas anxiousness may provoke symptoms so do other factors. The same type of criticism applies to the use of "effort syndrome." The term "psychoneurosis" implies, to many, "psychogenic disorders." This assumption is somewhat premature since crucial evidence as to what causes "psychoneurosis" has still to be presented. The same type of criticism applies to all the terms including the term "neurocirculatory asthenia" itself. We have retained

this term in our work for the same reason as the authors [43] who proposed it, namely, because it was "moderately descriptive and noncommittal."

Our patients were divided into two groups, those with chronic and those with acute disorder, on the basis of history alone. It was of interest, however, that when observations on various subjects were tabulated, scores made by patients with acute disease were nearer those of the control subjects than were the scores made by patients with chronic disease. Whether the former patients had a milder form of the same disorder or an entirely different one we do not know.

In the physiologic investigation, studies made with the patients at rest revealed few abnormalities. As the work stress was greater, the evidence of abnormality increased, the deviation from normal being most marked when the stress was maximal. It is possible that the same pattern of findings might be demonstrated by the experimental use of forms of stress other than muscular work, such as emotion-provoking stimuli or situations. However, we emphasized tests of muscular work in this investigation because of immediate practical relevance and because we were unable to devise relevant and quantitatively standardized emotion-provoking situations.

The interest in neurocirculatory asthenia during wars should be commented on, since the major work in this field was done then. It seems probable that the chronic type of the disorder at least is a common one featured by remissions and exacerbations. If the exacerbations are really provoked, as patients believe, by unaccustomed muscular work, emotion-provoking situations, exposure, infectious disease and the convalescent state, the circumstances of war provide almost experimental conditions for exacerbations. However, the exact importance of these various factors has as yet not been studied quantitatively or experimentally in previous wars or in this one. Neurocirculatory asthenia was common in this war too, although its true incidence was obscured by its many labels.

No specific effective cure has been developed. Our studies certainly do not add to this aspect. It is possible that specific therapy may be forced to await discovery of causal or fundamental mechanisms in the disorder. Evaluation of therapeutic claims must be based on knowledge of the clinical course of the disorder and on awareness of the fact that it is characterized by remissions as well as by exacerbations.[43a]

## SUMMARY

The present paper summarizes the major positive findings in a five year study of neurocirculatory asthenia, effort syndrome or anxiety neurosis. In successive sections the following points are made:

43. Oppenheimer, B. S.; Levine, S. A.; Morison, R. A.; Rothschild, M. A.; St. Lawrence, W., and Wilson, F. N.: Report on Neurocirculatory Asthenia and Its Management, Mil. Surgeon **42**:409, 1918.

43a. Cohen and others.[1a] Wheeler and others.[42a]

1. Terminology concerning this disorder is confused, with no satisfactory distinction between neurocirculatory asthenia, anxiety neurosis, effort syndrome, neurasthenia, psychoneurosis, combat fatigue and other terms.

2. Symptoms are multiple and high in incidence. In contrast, physical signs are few.

3. Studies of muscular work demonstrate short duration of performance in hard work and a defect in aerobic metabolism in all grades of work as evidenced by oxygen consumption and blood lactate concentration. Pulmonary ventilation is abnormal during work, as is ventilatory efficiency.

4. Ventilation index and awareness of dyspnea are abnormal.

5. The pulse rate for all grades of exercise is abnormally high. The capillaries of finger nail folds are abnormal. The size of the heart, the electrocardiograms and the resting circulatory measurements, including cardiac output, are normal.

6. Quantitative studies of pain and discomfort show abnormal reaction to painful stimuli.

7. Psychologic tests place patients with neurocirculatory asthenia in the "neurosis" category.

8. The incidence of neurocirculatory asthenia is high in mothers, fathers, brothers and sisters of patients with the disorder. If the disorder is hereditary, the data suggest mendelian dominance.

9. The cause, anatomic changes and specific treatment are obscure.

10. The symptoms, onset and exacerbations are influenced, according to patients' biographic reports, by muscular work, emotion-provoking situations, infection or nothing at all. The difficulties in interpreting this type of data are emphasized.

11. A convenient distinction was made on the basis of history alone between acute and chronic neurocirculatory asthenia. In this study "acute" refers to the disease in patients with a convincing history of previous health and ability to do hard work. "Chronic" refers to the disease in patients who had never been able to do hard work or athletics.

12. In all studies in which differences existed between patients and healthy controls mean values for those with the acute form of the disease fell between those for controls and those for patients with the chronic form.

13. It is emphasized in studies of this disorder, and perhaps in many others, that basal measurements made with the patients resting may not show abnormalities while measurements made while the patients are under stress may; the stronger the stress the greater the deviation from normal.

# EFFECT OF LANATOSIDE C ON THE CIRCULATION OF PATIENTS WITH CONGESTIVE FAILURE

## A Study Using Catheterization of the Right Side of the Heart

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THE METHOD of catheterization of the right side of the heart has made it practical to measure the cardiac output by the Fick principle in patients acutely ill with congestive failure. The purification of digitalis glucosides has made it safe to give a therapeutically effective dose of digitalis in a single intravenous injection. It is now possible in a few hours to make observations on the circulation before and after the drug has had its effect. Such observations are much easier to interpret than those made at intervals of one day or longer. The purpose of this paper is to report the data on changes in circulation produced by the intravenous administration of 1.6 mg. of lanatoside C in 22 patients with congestive heart failure.

### METHOD

The patients were studied either immediately after their admission to the hospital or on the following morning. Food was withheld for twelve hours before the observations if the patient was in the hospital. Those studied on entry to the hospital had been too ill to eat much food on the day of admission. Patients received morphine if dyspnea was severe, and many of them were supported by a back rest which raised the trunk to an angle of about 30 degrees.

The right side of the heart was catheterized by the method previously described.[1] In most instances the sample of mixed venous blood was obtained from the

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From the Department of Medicine, Emory University School of Medicine, Atlanta, Ga., and the Department of Medicine, Duke University School of Medicine, Durham, N. C.

1. Berconsky, I.: El volumen circulatorio per minute en el estado normal y patologico, Semana méd. **2**:570, 1930. Cournand, A., and Ranges, H. A.: Catheterization of the Right Auricle in Man, Proc. Soc. Exper. Biol. & Med. **46**:462, 1941. Warren, J. V.; Stead, E. A., Jr., and Brannon, E. S.: The Cardiac Output in Man: A Study of Some of the Errors in the Method of Right Heart Catheterization, Am. J. Physiol. **145**:458, 1946.

right auricle; in a few it was obtained from the right ventricle. Mixing may well be less complete in dilated hearts than in those of normal subjects. This problem was not investigated. Samples of arterial blood were obtained from the femoral artery. The oxygen content of the arterial and venous blood was measured by the method of Van Slyke.[2] The oxygen consumption was calculated from analysis of samples of expired air by the method of Haldene.[2] The cardiac output was calculated according to the Fick principle and recorded as liters per minute. The difficulty in computing surface areas in patients with varying degrees of edema makes the calculation of the cardiac index of less value.

The arterial pressure was recorded from the femoral artery by the method of Hamilton.[3] The mean atrial pressure was measured with a saline manometer, a point 5 cm. below the fourth costochondral junction being taken as a reference point. The peripheral resistance was recorded in absolute units and calculated from the formula:

$$R = \frac{Pm \text{ (mean pressure in mm. of Hg.)} \times 1{,}332}{CO \text{ (cardiac output in cc. per second)}}$$

Heparin was used as the anticoagulant for hematocrit readings.

None of the patients had received digitalis in the preceding three weeks. After the control observations were made, 1.6 mg. of lanatoside C was injected intravenously. There were no untoward reactions.

## RESULTS

All patients had had dyspnea on slight exertion and had had orthopnea before sedation. Peripheral edema was present in varying degrees, and the right atrial pressure was elevated in 21. Auricular fibrillation was present in 3 patients and paroxysmal auricular tachycardia in 2. The remainder had normal sinus rhythm. Patients with frank Cheyne-Stokes breathing were excluded from this series. In many, however, breathing was somewhat irregular and the values for oxygen consumption were less accurate than in normal subjects.

Thirteen patients had hypertension or coronary artery disease, 4 had rheumatic heart disease with mitral stenosis, 3 had syphilitic heart disease with aortic insufficiency and 2 had unclassified heart disease (1 with marked pulsus alterans and the other with auricular tachycardia).

The first observed effect was a fall in venous pressure, which began in five to ten minutes and continued for thirty to sixty minutes. The smallest fall was 20 mm. of water and the largest 135 mm., the average being 62 mm. The decrease in venous pressure was not preceded by diuresis and seemed to be independent of a decrease in

2. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2.

3. Hamilton, W. F.; Brewer, G., and Brotman, I.: Pressure Pulse Contours in the Intact Animal: I. Analytical Description of a New High-Frequency Hypodermic Manometer with Illustrative Curves of Simultaneous Arterial and Intracardiac Pressures, Am. J. Physiol. **107**:427, 1934.

blood volume. These observations are similar to those recorded by La Due.[4] The hematocrit reading fell during the period of observation in 14, remained unchanged in 6 and increased in 1. The fall in hematocrit reading may be the result of hemodilution caused by the fall in venous pressure. The total amount of blood drawn for measuring the cardiac output was not carefully determined, and it is possible that the fall was the result of repeated sampling.

The response of the cardiac rate was variable. In 6 patients the rate increased, in 2 it remained unchanged and in 14 it decreased. However, the stroke volume nearly always improved, being increased in 20 and lowered in only 2. There was no consistent change in oxygen consumption. The mean arterial pressure usually increased; it showed a rise of from 1 to 50 millimeters of mercury in 16 of the 20 patients in whom it was measured. The systolic pressure rose in the 20 patients in whom the measurement was made, the rise ranging from 4 to 50 millimeters of mercury. There was no consistent change in diastolic pressure. The peripheral resistance fell in eighteen of twenty observations.

The arteriovenous oxygen difference decreased in all but 1 instance. In 4 instances the decrease was 0.3 volumes per cent or less. These differences are not significant. In 16 the fall was 0.9 volumes per cent or greater. In 2 patients with marked anemia the fall was 0.5 volumes per cent, which is probably significant. Thus 18 of 22 had a significant narrowing of the arteriovenous oxygen difference. The cardiac index rose in twenty of the twenty-two observations. If the patients in whom the change in arteriovenous oxygen difference was not significant were eliminated, the increase in cardiac output would average 1.6 liters per minute, with a range of from 0.2 to 4.2 liters per minute.

## COMMENT

The data are surprisingly consistent. In patients with congestive failure lanatoside C produced a rise in cardiac output, an increase in stroke volume, a rise in systolic and mean arterial pressure and a fall in atrial pressure and in peripheral resistance. The determination of the cardiac output is based on the arteriovenous oxygen difference and on the quantity of oxygen removed from the lungs per minute. For this group of severely ill patients the determination of oxygen consumption was less reliable than the measurement of the arteriovenous oxygen difference. Therefore digitalis was not considered to have had a significant effect on the cardiac output in instances in which the arteriovenous difference did not show a significant decrease. The

4. La Due, J. S., and Fahr, G.: Effect of Intravenous Administration of Lanatoside C upon Output, Diastolic Volume, and Mechanical Efficiency of Failing Human Heart, Am. Heart J. **25**:344, 1943.

average increase in cardiac output in the 18 patients in whom the drug caused a fall in arteriovenous oxygen difference was 1.6 liters per minute. This was an increase in output of 2,300 liters, or 575 gallons, per twenty-four hours. It is no wonder that Withering was impressed by digitalis.

The increase in cardiac output occurred in patients with normal rhythm, paroxysmal auricular tachycardia and auricular fibrillation. The data support the thesis that digitalis has a direct effect on the strength of contraction of the ventricles and that its effect is not dependent on a reduction in cardiac rate.

The increase in cardiac output was accompanied with a rise in mean and systolic arterial pressures. This rise was not as great as it would have been if the peripheral vessels had not dilated. The data indicate that the fall in peripheral resistance was not sufficient to offset completely the effect on arterial pressure of a rise in cardiac output.

This study is of particular interest because of the information which it gives on the relation between the cardiac output and the development of congestive failure. In 3 patients (A. M., C. H. and T. W.) the cardiac output as related to surface area was increased in the presence of congestive failure. These patients were anemic, and the cardiac output even in the absence of failure would have been greatly increased.[5] When the heart began to fail the output dropped below the level needed by the body and the signs and symptoms of congestive failure developed. That this interpretation is correct and that the body was receiving too little blood even though the output was above the expected basal level is shown by the fact that in each patient the output was increased by the administration of lanatoside C. In 4 patients (D. W., K. Mc., C. Mc. and R. N.) the arteriovenous oxygen difference and the cardiac outputs as related to surface area were within the extremes of the normal range. Was the cardiac output adequate for the tissue needs? The finding of an increase with lanatoside C suggests that the output was not optimum for the needs of the body. Similar observations have been reported in regard to persons with pericardial tamponade. The cardiac output in certain instances of purulent pericarditis may be greatly increased. The fact that it is causing an inadequate circulation becomes obvious when the tamponade is relieved and the output climbs to still higher levels.[6]

5. Brannon, E. S.; Merrill, A. J.; Warren, J. V., and Stead, E. A., Jr.: The Cardiac Output in Patients with Chronic Anemia as Measured by the Technique of Right Atrial Catheterization, J. Clin. Investigation **24**:332, 1945.

6. Warren, J. V.; Brannon, E. S.; Stead, E. A., Jr., and Merrill, A. J.: Pericardial Tamponade from Stab Wound of the Heart and Pericardial Effusion or Empyema: A Study Utilizing the Method of Right Heart Catheterization, Am. Heart J. **31**:418, 1946.

*Effect of the Intravenous Injection of 1.6 Milligrams of Lanatoside C*

| Subject | | Age | Sex | Surface Area, Sq. M. | Oxygen Consumption, Cc. per Minute per Sq. M. | Arterial Saturation, % | Oxygen Content, Vol. % | | Arteriovenous Oxygen Difference, Vol. % | Cardiac Output, Liters per Min. | Stroke Volume, Cc. | Heart Rate | Arterial Pressure, Mm. Hg | | | Peripheral Resistance, Units | Atrial Pressure, Cc. of $H_2O$ | Hematocrit Reading |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Arterial | Mixed Venous | | | | | Systolic | Diastolic | Mean | | | |
| A. M. W. | Hypertensive heart disease, anemia, uremia | 39 | F | 1.38 | 138 | .. | 6.3 | 3.2 | 3.1 | 6.1 | 59 | 104 | 223 | 108 | 147 | 1,870 | 225 | 16 |
| | 1 hour after lanatoside C | | | | 148 | | 6.0 | 3.5 | 2.5 | 8.2 | 85 | 96 | 237 | 96 | 146 | 1,420 | 170 | 16 |
| C. B. H. | Hypertensive heart disease, anemia, uremia | 33 | F | 1.74 | 163 | .. | 7.2 | 4.1 | 3.1 | 9.2 | 92 | 100 | 266 | 133 | 185 | 1,610 | 125 | 19 |
| | 1 hour after lanatoside C | | | | 163 | | 7.2 | 4.6 | 2.6 | 11.0 | 81 | 136 | ... | ... | ... | ..... | 15 | 17 |
| C. P. | Heart disease, type unknown, auricular tachycardia | 43 | F | 1.80 | 113 | 94 | 14.7 | 6.0 | 8.7 | 2.3 | 13 | 178 | 102 | 82 | 83 | 2,890 | 185 | 38 |
| | 70 minutes after lanatoside C | | | | 119 | 95 | 14.0 | 10.7 | 3.3 | 6.5 | 92 | 71 | 150 | 80 | 105 | 1,290 | 50 | 35 |
| | 4 days later | | | | 108 | 94 | 14.9 | 10.2 | 4.7 | 4.1 | 68 | 60 | 144 | 74 | 95 | 1,850 | 25 | 37 |
| D. W. | Coronary arterial disease | 74 | M | 1.76 | 214 | .. | 13.5 | 7.0 | 6.5 | 5.8 | 39 | 150 | 159 | 110 | 124 | 1,700 | 75 | 32 |
| | 80 minutes after lanatoside C | | | | 214 | | 13.4 | 8.1 | 5.3 | 7.1 | 86 | 84 | 164 | 97 | 118 | 1,310 | 5 | 32 |
| T. S. | Rheumatic heart disease, mitral stenosis and auricular fibrillation | 54 | M | 1.85 | 123 | 91 | 14.4 | 6.5 | 7.9 | 2.9 | 24 | 120 | 108 | 80 | 86 | 2,390 | 215 | 38 |
| | 1 hour after lanatoside C | | | | 120 | | 11.7 | 6.9 | 4.8 | 4.6 | 68 | 68 | 128 | 75 | 88 | 1,470 | 155 | 35 |
| | 10 days later | | | 1.71 | 142 | | 14.6 | 9.7 | 4.9 | 4.9 | 64 | 76 | 133 | 72 | 89 | 1,440 | 55 | 35 |
| H. T. | Coronary arterial disease with auricular fibrillation | 73 | M | 1.57 | 139 | 83 | 15.4 | 8.3 | 7.1 | 3.1 | 31 | 100 | 130 | 87 | 95 | 2,940 | 250 | 45 |
| | 2 hours after lanatoside C | | | | 135 | | 15.3 | 8.5 | 6.8 | 3.1 | 27 | 116 | 157 | 99 | 113 | 3,590 | 230 | 45 |
| K. Mc. | Hypertensive heart disease, auricular fibrillation | 49 | F | 1.94 | 155 | .. | 18.8 | 13.4 | 5.4 | 5.6 | 75 | 75 | 198 | 96 | 123 | 1,760 | 113 | 52 |
| | 70 minutes after lanatoside C | | | | 163 | | 19.4 | 15.6 | 3.8 | 8.3 | 105 | 79 | 206 | 108 | 137 | 1,320 | 70 | 55 |
| H. S. | Syphilitic aortic insufficiency | 40 | M | 1.70 | 139 | .. | 14.1 | 6.5 | 7.6 | 3.1 | 33 | 94 | 212 | 51 | 97 | 2,500 | 245 | 40 |
| | 1 hour after lanatoside C | | | | 167 | | 14.1 | 7.6 | 6.5 | 4.4 | 47 | 94 | 237 | 56 | 105 | 1,910 | 190 | 39 |
| J. H. | Syphilitic aortic insufficiency | 42 | M | 1.92 | 182 | .. | 16.6 | 5.8 | 10.8 | 3.2 | 38 | 84 | 202 | 73 | 112 | 2,800 | 150 | 44 |
| | 70 minutes after lanatoside C | | | | 137 | | 14.8 | 7.0 | 7.8 | 3.4 | 47 | 72 | 226 | 67 | 113 | 1,700 | 145 | 40 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H. H. | Syphilitic aortic insufficiency.. | 46 | M | 2.0 | 225 | .. | 16.7 | 6.1 | 10.6 | 4.2 | 42 | 100 | 303 | 86 | 151 | 2,810 | 160 | 48 |
| | 50 minutes after lanatoside C.. | | | | 204 | | 15.9 | 7.3 | 8.6 | 4.7 | 45 | 104 | 298 | 89 | 158 | 2,690 | 70 | 46 |
| R. A. W. | Hypertensive heart disease... | 49 | M | 1.90 | 126 | .. | 14.9 | 7.6 | 7.3 | 3.3 | 32 | 104 | 147 | 102 | 114 | 2,760 | 120 | 39 |
| | 50 minutes after lanatoside C.. | | | | 122 | | 14.5 | 10.0 | 4.5 | 5.1 | 69 | 74 | 155 | 84 | 99 | 1,550 | 50 | 37 |
| L. H. | Hypertensive heart disease, anemia, uremia ..... | 40 | F | 1.58 | 108 | .. | 8.5 | 4.0 | 4.5 | 3.8 | 43 | 88 | 227 | 128 | 162 | 3,430 | 210 | 20 |
| | 70 minutes after lanatoside C.. | | | | 113 | | 8.4 | 4.8 | 3.6 | 5.0 | 57 | 88 | 276 | 138 | 189 | 3,000 | 165 | 20 |
| F. M. | Hypertensive heart disease... | 51 | M | 1.96 | 173 | 81 | 13.9 | 5.5 | 8.4 | 4.0 | 47 | 86 | 208 | 133 | 155 | 3,080 | 250 | 41 |
| | 1 hour after lanatoside C..... | | | | 159 | 82 | 13.7 | 6.8 | 6.9 | 4.5 | 60 | 75 | 225 | 143 | 194 | 3,450 | 185 | 40 |
| C. Mc. | Hypertensive heart disease... | 63 | M | 1.82 | 166 | .. | 15.2 | 9.0 | 6.2 | 4.9 | 52 | 94 | 200 | 130 | 152 | 2,470 | 135 | 42 |
| | 70 minutes after lanatoside C.. | | | | 182 | | 14.1 | 9.4 | 4.7 | 7.0 | 83 | 84 | 228 | 127 | 160 | 1,420 | 30 | 40 |
| T. W. | Hypertensive heart disease, anemia, uremia ..... | 35 | M | 1.67 | 150 | 96 | 5.2 | 3.0 | 2.2 | 11.4 | 130 | 88 | 150 | 100 | 125 | 880 | 300 | 14.4 |
| | 60 minutes after lanatoside C.. | | | | 149 | | 4.9 | 3.0 | 1.9 | 13.1 | 146 | 90 | 174 | 98 | 136 | 830 | 260 | 13.7 |
| J. G. | Rheumatic heart disease, mitral stenosis ..... | 30 | M | 1.75 | 121 | 92 | 15.0 | 5.4 | 9.6 | 2.2 | 18 | 124 | 137 | 97 | 105 | 3,780 | 215 | 43 |
| | 60 minutes after lanatoside C.. | | | | 137 | | 14.8 | 6.1 | 8.7 | 2.7 | 23 | 120 | 142 | 96 | 106 | 3,140 | 165 | 41 |
| | 3 weeks later..... | | | 1.53 | 143 | 91 | 18.6 | 11.2 | 7.4 | 3.0 | 33 | 92 | 128 | 82 | 97 | 2,580 | 45 | 49 |
| L. H. | Rheumatic heart disease, mitral stenosis ..... | 41 | M | 1.91 | 149 | 79 | 13.7 | 7.3 | 6.4 | 4.4 | 43 | 104 | 116 | 72 | 80 | 1,460 | 195 | 42 |
| | 60 minutes after lanatoside C.. | | | | 169 | | 13.3 | 7.1 | 6.2 | 5.2 | 45 | 116 | 129 | 77 | 91 | 1,400 | 170 | 40 |
| | 24 days later..... | | | 1.74 | 141 | 89 | 13.2 | 6.4 | 6.8 | 3.6 | 39 | 92 | 120 | 79 | 87 | 1,930 | 150 | 36 |
| N. J. | Rheumatic heart disease, mitral stenosis ..... | 39 | F | 2.22 | 176 | .. | 12.5 | 4.5 | 8.0 | 4.9 | 44 | 112 | 195 | 88 | 126 | 2,000 | 300 | 38 |
| | 90 minutes after lanatoside C.. | | | | 108 | | 12.5 | 4.4 | 8.1 | 3.0 | 28 | 108 | ... | ... | ... | ..... | 260 | 38 |
| R. N. | Myocardial infarction ..... | 40 | F | 1.67 | 153 | .. | 10.8 | 6.0 | 4.8 | 5.3 | 47 | 112 | 64 | 44 | 50 | 750 | 150 | 34 |
| | 60 minutes after lanatoside C.. | | | | 166 | | 10.6 | 7.3 | 3.3 | 8.4 | 80 | 105 | 81 | 50 | 63 | 600 | 120 | 34 |
| A. P. | Etiology unknown ..... | 40 | M | 1.90 | 109 | 85 | 14.4 | 6.4 | 8.0 | 2.6 | 25 | 104 | 89 | 66 | 69 | 2,140 | 290 | 42 |
| | 60 minutes after lanatoside C.. | | | | 114 | 84 | 14.2 | 9.0 | 5.2 | 4.2 | 46 | 92 | 113 | 67 | 80 | 1,520 | 195 | 42 |
| | 12 days later..... | | | 1.71 | 144 | | 17.2 | 12.2 | 5.0 | 4.9 | 53 | 92 | 127 | 81 | 96 | 1,560 | 80 | 48 |
| E. M. | Coronary arterial disease..... | 33 | M | 1.96 | 153 | .. | 15.1 | 7.8 | 7.3 | 4.1 | 37 | 111 | 158 | 97 | 119 | 2,330 | 270 | 46 |
| | 75 minutes after lanatoside C.. | | | | 153 | | 14.8 | 8.8 | 6.0 | 5.0 | 60 | 84 | 182 | 100 | 127 | 2,040 | 200 | 44 |
| A. W. | Coronary arterial disease..... | 58 | M | 2.1 | 145 | 90 | 17.2 | 7.7 | 9.5 | 3.2 | 28 | 112 | 137 | 100 | 108 | 2,710 | 220 | 47 |
| | 60 minutes after lanatoside C.. | | | | 143 | | 16.4 | 8.5 | 7.9 | 3.8 | 35 | 108 | 140 | 100 | 108 | 2,280 | 170 | 45 |

These observations stress again the fact that the adequacy of the output of the heart must be determined in relation to the needs of the body for blood. If the need is low, as in myxedema,[7] a considerable reduction in cardiac output may occur without the development of the signs and symptoms of congestive failure. If the needs of the body are great, as in exercise[8] or hyperthyroidism, congestive failure may occur with a high output. When the heart is unable to pump sufficient blood to supply all the tissues, the renal blood flow is sharply reduced, the filtration rate falls and sodium retention occurs. This sequence of events may occur with any absolute value for cardiac output.

The fall in venous pressure could not be correlated with the magnitude of the increase in cardiac output. In certain patients the venous pressure fell to normal levels within one hour. In others the pressure fell during the first hour but leveled off at an abnormally high value and did not fall to normal during the period of observation. It has been pointed out that the venous pressure is greatly influenced by two factors in cardiac failure: (1) the tone of the vascular bed and (2) the blood volume.[9] In chronic heart failure both the blood volume and the tone of the vascular system are increased. There is considerable vasoconstriction in the kidneys, the peripheral resistance is raised and the venous pressure is increased. The first two of these changes occur in reversible shock from hemorrhage. The third is absent because even intense vasoconstriction cannot raise the venous pressure if the blood volume is greatly decreased. The vascular constriction in heart failure and in acute hemorrhage probably results from the fact that in both the cardiac output is reduced. Whether the constriction is humoral or reflex or both has not been determined. Digitalis, when effective in improving the circulation, reduces the tone in the vascular bed. The blood flow to the kidneys increases, the peripheral resistance falls and the venous pressure drops. Whether these changes in vascular tone occur because of the improvement in cardiac output alone or whether they are in part the result of a peripheral action of lanatoside C itself has not been determined. The primary fall in atrial pressure appears to be related to the changes in venous tone just described. The further fall in venous pressure which may occur during the next few days appears to be related to the decrease in blood volume caused by the diuresis.

7. Unpublished data.

8. Hickam, J. B., and Cargill, W. H.: Effect of Exercise on Cardiac Output and Pulmonary Arterial Pressure in Normal Persons and in Patients with Cardiovascular Disease and Pulmonary Emphysema, to be published.

9. Warren, J. V., and Stead, E. A., Jr.: Fluid Dynamics in Chronic Congestive Heart Failure, Arch. Int. Med. **73**:138 (Feb.) 1944.

McMichael and Sharpey-Schafer [10] have called attention to the fact that lowering of the venous pressure by pooling of blood in the extremities will cause an increase in cardiac output in certain persons with congestive heart failure. They have emphasized the fall in venous pressure produced by intravenous administration of digoxin and have suggested that the major benefits of digoxin treatment result from a peripheral action on venous pressure. Other authors,[11] reporting on the effects of ouabain, have found no correlation between the effect on venous pressure and the rise in cardiac output. The data reported here likewise show no relationship between the magnitude of the fall of venous pressure and the degree of increase in cardiac output. Observations on the effects of venesection from this laboratory indicate that in patients with congestive failure a fall in venous pressure may be accompanied with a rise in cardiac output.[7] Recent observations by Hickam and Cargill [8] on the effects of exercise on the cardiac output of patients with congestive failure are helpful in the interpretation of these findings. During exercise the cardiac output in patients with severe congestive failure may fall below the resting level. The heart in these patients is inadequate at rest. When pushed harder it becomes even less adequate. When the exercise stops the cardiac output presumably returns eventually to the resting level, though studies were not made after exercise. These observations indicate that in the presence of heart failure any procedure that normally decreases the work of the heart may instead result in an actual increase in output. Lowering the venous pressure by venesection tends to reduce pulmonary congestion, diminish reflex activity and in certain instances lower the arterial pressure. These effects may well reduce the requirements of the body for blood. In severe carditis decreasing the work required of the heart by venesection may well cause a rise, rather than a fall, in cardiac output.

The data recorded here on the effect of lanatoside C on the circulation are much more consistent than those recorded on the use of the slower-acting oral preparations of digitalis. This was to be expected because, as previously pointed out, the output of the heart at rest may rise, fall or remain unchanged over a period of several days while the patient is compensating.

The cardiac output in congestive failure may be classified as follows:

1. The output is low on the patient's admission to the hospital, and it remains low. Compensation results entirely from the use of salt

10. McMichael, J., and Sharpey-Schafer, E. P.: The Action of Intravenous Digoxin in Man, Quart. J. Med. **13**:123, 1944.

11. Bloomfield, R. A.; Rapoport, B.; Milnor, J. P.; Long, W. K.; Mebane, J. G., and Ellis, L. B.: The Effect of Ouabain on the Dynamics of the Circulation in Patients with Congestive Heart Failure, J. Clin. Investigation, to be published.

restriction and mercurial diuretics. Edema will develop if the patient is placed on a normal diet.

2. The output is low on the patient's admission to the hospital, and it increases on digitalization. Compensation occurs without the use of salt restriction or diuretics.

3. The output is normal on the patient's admission to the hospital, and it remains normal while he is confined to bed. It is adequate for the resting state but inadequate in the presence of activity or infection. The symptoms on admission to the hospital result from waterlogging and congestion in the lungs which occurred during activity or were precipitated by an infection. Reduction of activity or clearing of infection allows adequate output at rest. Signs and symptoms disappear as long as activity is sharply restricted.

4. The output is high on the patient's admission to the hospital, and it falls with compensation. The output is increased over the normal resting level because of anxiety, discomfort or some associated disturbance such as anemia, beriberi or arteriovenous fistula. It is higher than the normal basal level but not high enough to meet the needs of the body. If the demands of the body for blood are lowered, the resting cardiac output decreases as compensation occurs.

It is clear that the results from rapid and slow digitalization would cause no confusion in groups 1, 2 and 3. No patients in the series reported here fell in group 3. The findings in group 4 will differ by the two methods. If a restless, apprehensive patient with moderate failure is studied, the output on his admission to the hospital may be high. If digitalization is rapidly carried out, the fact that the output is still not high enough for the state of the patient will become obvious as the output rises to a still higher level with digitalization. Since the output is now adequate for the needs of the patient, the signs and symptoms of congestive failure will disappear. The patient loses his restlessness and apprehension, and the requirement of the body for blood decreases. The cardiac output therefore falls. The higher output on his admission to the hospital was inadequate for body needs; the lower output is now adequate, and the signs and symptoms of congestive failure do not recur.

The initial rise in output produced by digitalization may be completely overlooked unless observations are made within a short time after the effect of digitalis has occurred. Similar results are seen in patients with congestive failure and severe anemia. The output is high but not high enough for the body needs, and failure occurs. Digitalization causes a further rise in output. When the anemia is corrected, the cardiac output falls below the level present before digitalization.

## SUMMARY AND CONCLUSIONS

1. The effect of the intravenous injection of 1.6 mg. of lanatoside C on the circulation in 22 patients with congestive heart failure was observed. The right side of the heart was catheterized in order to obtain samples of mixed venous blood and to measure the right atrial pressure.

2. The first measurable effect of lanatoside C was on the atrial pressure. The average fall during the first sixty to one hundred and twenty minutes was 62 mm. of water.

3. In 18 of the 22 subjects the cardiac output increased significantly. The average increase was 1.6 liters per minute. This represents an increase in blood flow to the tissues of 2,300 liters per day.

4. There was no consistent change in oxygen consumption. The increase in output resulted primarily from a decrease in arteriovenous oxygen difference.

5. The systolic and mean arterial pressures rose and the peripheral resistance fell.

6. The response of the cardiac rate was variable, but in 20 of the patients the stroke volume increased.

7. Patients with severe anemia and congestive heart failure may have a high cardiac output. Digitalis may cause a still further increase in output.

8. Certain patients with congestive heart failure have an insufficient cardiac output though the cardiac index and the arteriovenous oxygen difference are within the extreme limits of normal. That the output is inadequate is suggested by the increase which occurs with digitalization.

9. The data indicate that lanatoside C increases the output of the heart in the presence of a normal rhythm and that the prime action of digitalis is on the ventricular muscle, which enables the ventricles to increase their output.

# PLACE OF INTERMITTENT VENOUS HYPEREMIA IN THE TREATMENT OF OBLITERATIVE VASCULAR DISEASE

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IN A PREVIOUS communication, Hick, Coulter and one of us[1] summarized the reasons which prompted the use of intermittent venous hyperemia in cases of obliterative vascular disease. At that time (1937) the number of patients who had used this treatment was small, and they had not used the method originally advocated by Collens and Wilensky[2] for a long time. The conclusions were tentative.

The rationale of this treatment has remained controversial, and there are still a number of vascular clinics in which its efficacy is doubted.[3] Others employ it when the extremity is obviously lost and waste valuable time or hasten the absorption of toxins from gangrenous toes.

The purpose of this communication is to present our indications for this form of treatment and the results obtained from it. This report is based on 100 consecutive unselected cases taken from the office files, and it excludes all patients who have had other types of treatment, especially sympathectomy, although, as will be pointed out, the method is routinely used after sympathectomy for occlusive vascular disease, after embolectomy and after amputation of one limb for the protection of the other.

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1. de Takats, G.; Hick, F. K., and Coulter, J. S.: Intermittent Venous Hyperemia in Treatment of Peripheral Vascular Disease, J. A. M. A. **108**:1951 (June 5) 1937.

2. Collens, W. S., and Wilensky, N. D.: The Use of Intermittent Compression in the Treatment of Peripheral Vascular Disease, Am. Heart J. **11**:705, 1936.

3. Allen, E. V., and McKechnie, R. D.: Effect of Intermittent Venous Occlusion on the Circulation of the Extremities, J. Lab. & Clin. Med. **22**:1260, 1937. Veal, J. R., and McLord, W. M.: Blood Oxygen Changes Following Intermittent Venous Occlusion, Am. Heart J. **17**:401, 1939. Harpuder, K., and Stein, I. D.: Therapeutic Value of Passive Hyperemia in Peripheral Vascular Disease, Arch. Phys. Therapy **20**:9, 1939. Abramson, D. I.; Zozeela, H., and Schkloven, N.: The Vasodilating Action of Various Therapeutic Procedures Which Are Used in the Treatment of Peripheral Vascular Disease: A Plethysmographic Study, Am. Heart J. **21**:756, 1941.

## METHODS OF STUDY

The grade of obliterative vascular disease is always determined before treatment is instituted. In a previous communication, Beck, Roth and one of us [4] emphasized the point that all therapeutic methods tested should be correlated with the stage of the occlusive vascular disease during which they are undertaken. This is true of intermittent venous hyperemia as it is of sympathectomy.[5] The four stages may be summarized as follows:

Grade 1. The patients have diminished or absent pulsations of the foot or the lower part of the leg. The skin is warm, and the color of the feet is normal. They can walk a distance of two to six blocks without pain.

Grade 2. The feet of the patients in this stage are pulseless, and they are unable to walk a distance of two blocks without pain. However, trophic changes may still be absent although the feet are cold and dry, and a single toe is often cyanotic. A cold and moist foot, incidentally, always indicates a better prognosis because the patients exhibit a heightened sympathetic tone, the release of which warms up their skin.

Grade 3. Pain at rest and intractable ischemic neuritis are present at this stage. Walking may be less painful, or it may even offer relief when rest in bed is difficult. When the foot is ice cold and when arteriolar obstruction and capillary paralysis are obvious from the pronounced dependent rubor, sympathectomy is of no use and may precipitate gangrene.

Grade 4. The patients exhibit ulceration and gangrene of the digits or of parts of the foot. The lesion is dry and not too painful. There is no evidence of infection. The popliteal pulse is absent, and possibly the femoral pulse is also absent. Supracondylar amputation at the level of positive histamine flares used to be the surgical procedure of choice for these patients. However, a sympathetic block may so shift the level of circulatory efficiency that amputation of the lower part of the leg or a midmetatarsal amputation can be tolerated.

Next, the amount and duration of constriction is determined by inflating a blood pressure cuff at the mid-thigh to a subdiastolic pressure, usually 60 mm. of mercury, and maintaining this pressure until a maximal distention of the dorsal veins and a satisfactory rubor of the toes appear. Obviously the more severe the vascular lesion, the longer it will take for the capillaries to dilate and for the veins to fill. If more than four minutes are required for this purpose, the patient must have a severe arterial and arteriolar obstruction, and the fate of the limb is doubtful. In patients with visible signs of venous stasis, cyanosis of toes, the pressure should not exceed 40 mm. of mercury, and the cuff should not be kept on longer than is necessary to produce a rubor. The duration of the release of pressure should be as long as it takes for the foot (or hand) to take on the color and the venous filling which it exhibited prior to constriction. In our experience, this never takes longer than one minute, but a slight elevation of the treated extremities on a pillow facilitates the drainage of trapped blood. Heating the abdomen with a cradle helps to diminish the vasomotor tonus in the extremity.

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4. de Takats, G.; Beck, W. C., and Roth, E. A.: The Neurocirculatory Clinic: A Summary of Its Activities, Ann. Int. Med. **13**:957, 1939.

5. de Takats, G.; Risley, T. C.; Jordan, P., and Fowler, E. F.: Sympathectomy in the Treatment of Peripheral Vascular Sclerosis, J. A. M. A. **131**:495 (June 8) 1946.

The factors observed before the constrictor is prescribed are as follows: rate of pulse, color of feet, the drop in the temperature of the skin, venous filling time, oscillometric curves, walking ability and the rise in the temperature of the skin after sympathetic block. General cardiovascular tests, including determinations of the blood sugar, blood cholesterol and nonprotein nitrogen contents and electrocardiographic and concentration-dilution tests, are always included. Of these tests, a few need further comment. Walking ability is determined by having the patient walk on level ground (in a corridor) at a rate of ten paces in ten seconds until the muscles of the calf begin to ache or the toes become numb. It is perfectly clear that this ability varies a great deal in the same patient from day to day, depending on the temperature of the room, on the ground he is walking on (whether cement or grass) and on premedication. Acetylsalicylic acid, pentobarbital sodium and narcotics will prolong the period before claudication develops. Nevertheless it is still the simplest and most useful of all tests and one that the patient can report on later when returning for follow-up examinations.

The venous filling time described by Collens and Wilensky [6] has been modified as follows. The limb to be examined is elevated to empty the superficial veins on the dorsum of the foot and to relieve it of any cyanosis or rubor. A blood pressure cuff is placed on the thigh of the patient and inflated to 60 mm. of mercury while the leg is still elevated. The leg is then put in the horizontal position, and the foot is placed under adequate natural or artificial light. The time of venous compression is noted and also the time it takes for the dorsal veins to be raised from the skin level, after which they may show venous pulsation. This end point is not always easy to read; for normal healthy persons, not more than five to ten seconds are sufficient to produce venous stasis, and for patients with severe arterial obliteration, two to six minutes may elapse before adequate venous filling is observed. The test is made at room temperature, and the comparative values from the two sides are especially significant. This is really a rough circulation time and perhaps is the best clinical test for any detectable improvement after treatment with intermittent venous hyperemia. The duration of stasis is always much shorter than the duration of constriction, since during the latter a stretching of the venocapillary bed is the object.[1]

Temperatures of the skin are determined with a small portable electric thermometer, again at room temperature, before and after sympathetic block. A good rise in the temperature and a markedly increased walking ability speak for the advisability of sympathectomy if other parts of the cardiovascular apparatus are not notably involved. When there is a poor response to sympathetic block or if there is marked coronary, cerebral or renal involvement, the constrictor substitutes for sympathectomy. Thus, the data reported here deal with patients in advanced stages of the disease.

### INDICATIONS FOR THE USE OF INTERMITTENT VENOUS HYPEREMIA

1. Intermittent venous hyperemia is indicated after acute arterial occlusion if embolectomy or sympathectomy is not feasible or after any one of these operations as postoperative treatment. If venous thrombosis is present, the treatment may increase edema or facilitate embolization. However, in many hundreds of cases we have not actually seen

6. Collens, W. S., and Wilensky, N. D.: Two Quantitative Tests of Peripheral Vascular Obstruction, Am. J. Surg. 34:71, 1936.

this happen. In cases of minor emboli, sympathetic block combined with the use of a rhythmic constrictor may make an embolectomy unnecessary, but if the patient is seen within the first ten hours embolectomy is always preferable. For acute thromboses, sympathetic block combined with venous hyperemia and the use of papaverine for the relief of pain and heparin to prevent spreading of thrombosis constitute our choice of methods.[7] When a sudden thrombosis, with peripheral embolization, has taken place in sclerotic patients with popliteal aneurysms, sympathectomy and intermittent venous hyperemia should precede the obliteration of the sac; at least a six week treatment is advisable before a direct attack on the aneurysm is undertaken.

2. Intermittent venous hyperemia is indicated for patients with chronic arterial occlusions due to arteriosclerosis with and without diabetes, to syphilis or to thromboangiitis obliterans. Many of these patients do well if they are subjected to sympathectomy, particularly if the operation is carried out in the early stages. Patients with thromboangiitis obliterans, unless they are in the late "burned out" stage, exhibit considerable vasospasm, and, as pointed out in our first communication,[1] intermittent venous compression may aggravate such spasm. Therefore, all patients with obliterative vascular disease exhibiting vasospasm first are subjected to sympathectomy before the described treatment is begun. In cases of ischemic and diabetic neuropathy, venous hyperemia seems to be of no avail; in fact, it often aggravates the pain.

### CONTRAINDICATIONS

From what has been said in the foregoing paragraphs, it is obvious that we advise against the use of the apparatus (1) in acute venous thrombosis, (2) in lymphangitis, (3) in severe arteriolar obstruction and (4) in the presence of frank gangrene. In addition, the treatment has been found useless for neuropathies, whether ischemic or metabolic, causalgic states, sequelae of frost bite, trench foot or immersion limb. To establish such treatment when other methods are available or necessary seems a grave error.

### RESULTS OF TREATMENT

For the clinical evaluation of this treatment, we have selected 100 cases in which no other form of treatment was employed. Even in such cases, as Silbert has pointed out,[8] there is a natural course of

7. de Takats, G.: Surgical Treatment of Acute Vascular Occlusions, S. Clin. North America **22**:199, 1942.

8. Silbert, S.: Evaluation of Results in Treatment of Peripheral Circulatory Disease, Am. Heart J. **15**:255, 1938.

slow improvement unless some acute vascular accident is superimposed on the chronic arterial insufficiency. Nevertheless, our records indicate an unmistakable benefit to be derived by the properly selected patient. After the preliminary tests, the patients are instructed to rent or buy an automatic apparatus, use it at home for two or three hours daily and then report every three months for the first year, twice a year for the second year and once the third year. Our data have been collected on the basis of these observations; the patients stay at work and use the equipment in the morning and in the evening or at night.

Of the 100 patients, 15 were women and 85 were men. Table 1 summarizes the results, which are grouped according to four grades. We noted in our records that subjective improvement was registered in a higher percentage than objective improvement. This may be due to autosuggestion, but in a few carefully studied cases it was simply because of the fact that the tests routinely employed were not capable of detecting small differences. Thus, circulation times determined with

TABLE 1.—*Results of Treatment in 100 Patients*

| Results | Number of Patients * |
|---|---|
| Notable improvement | 35 |
| Slight improvement | 32 (2) |
| No change | 28 (5) |
| Worse | 5 (3) |

* Figures in brackets indicate the number of diabetic patients.

the fluorescein quartz lamp[9] showed improvement when the other methods revealed no change. The subject of the patient's peace of mind will be discussed later. For the sake of uniformity, however, improvement was only noted when one or several of our tests indicated it; subjective improvement without objective evidence of improvement was disregarded (table 1).

According to this table, 67 patients derived some benefit whereas 33 patients either showed no improvement or had a progression of the disease. For such a heterogenous group of patients as these, the figures require further analysis. For the sake of brevity only some of the more obvious factors have been analyzed. The grading of peripheral vascular involvement is shown in table 2. One notes that 71 patients had an advanced degree of obliteration, and this is to be expected since our indications call for more active types of therapy, notably sympathectomy, for patients in the earlier stages of the disease. The duration of treatment as it influenced results has also been of interest, and table 3 indicates that approximately two thirds of the 100 patients had

9. Lange, K., and Boyd, L. J.: The Use of Fluorescein to Determine the Adequacy of the Circulation, M. Clin. North America **26**:943, 1942.

less than one year of treatment whereas one third continued to use the apparatus for over one year. The figures are small, but the percentage of failures after one year is about one third of that observed among patients who stopped the treatment before the year was over. There are, of course, several factors here which cloud the issue. The fact that the patients continued treatment for more than a year indicates that they had a favorable response earlier since otherwise they would have discontinued it. The patients were told not to continue treat-

TABLE 2.—*The Severity of Vascular Disease in 100 Patients*

| | |
|---|---|
| Grade 1 | 2 |
| Grade 2 | 27 |
| Grade 3 | 41 |
| Grade 4 | 30 |
| | 100 |

TABLE 3.—*Results as Influenced by Duration of Treatment*

| Duration of Treatment | Number of Cases | | No Improvement | | Percentage Not Improved | |
|---|---|---|---|---|---|---|
| 1 to 3 mo. | 28 | | 11 | | 39 | |
| 3 to 6 mo. | 17 | 67 | 9 | | 53 | 41 |
| 6 to 12 mo. | 22 | | 7 | | 32 | |
| 1 to 3 yr. | 21 | | 6 | | 29 | |
| 3 to 6 yr. | 11 | 33 | 2 | | 18 | 15 |
| More than 6 years | 1 | | .. | | 0 | |
| | 100 | | 35 | | | |

TABLE 4.—*Results as Influenced by Diabetes*

| Case | Age | Grade | Subjective Relief | Objective Relief | Worse |
|---|---|---|---|---|---|
| A.B. | 58 | 3 | None | None | .. |
| G.A. | 65 | 3 | None | None | + |
| R.T. | 53 | 3 | None | None | + |
| S.D. | 48 | 4 | None | None | .. |
| S.I. | 50 | 4 | Moderate | Slight | .. |
| L.L. | 65 | 3 | None | None | .. |
| O.S. | 51 | 2 | None | None | .. |
| S.B. | 65 | 4 | Slight | None | .. |
| M.B. | 55 | 2 | Slight | Slight | .. |
| R.S. | 48 | 4 | None | None | + |

ment if after one or two months there was no subjective improvement. On the basis of table 3, we are inclined to believe that such treatment, once it is clearly indicated and prescribed, should be continued for one year before it is permanently given up.

We have already stated that diabetic arteriosclerosis, especially when associated with diabetic neuropathy, responds poorly to intermittent venous hyperemia. In table 4 we have listed data on 10 diabetic patients, all of whom have used this treatment for at least three months.

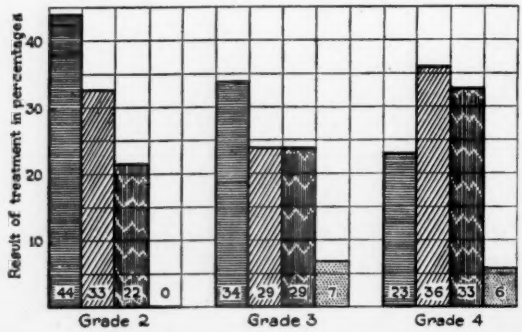
Only 2 of the 10 have shown objective improvement. In a number of other cases, not included here, the treatment was discontinued after a few days because of continuous pain or lancinating, pseudotabetic pain.

Table 5 shows the degree of improvement in the 100 cases according to the four grades of severity of the disease. If the 2 patients with grade 1 disease, who both did well, are disregarded, one can say that with advancing degree of obliteration fewer patients can expect decided improvement. Roughly speaking, a little less than one half of the patients with grade 2 disease showed considerable improvement (12 of

TABLE 5.—*Results as Influenced by Stage of Vascular Disease*

| Grade | Number of Cases | Notable Improvement | Slight Improvement * | No Change * | Worse * |
|---|---|---|---|---|---|
| 1 | 2 | 2 | .. | .. | .. |
| 2 | 27 | 12 | 9 (1) | 6 (1) | .. |
| 3 | 41 | 14 | 12 | 12 (1) | 3 (2) |
| 4 | 30 | 7 | 11 (1) | 10 (3) | 2 (1) |
| | 100 | 35 | 32 (2) | 28 (5) | 5 (3) |

* Figures in brackets indicate the number of diabetic patients.




Results of the use of a rhythmic constrictor for the production of intermittent venous hyperemia. Note that for grade 2 disease the percentage of improvement is higher than for grade 3 disease and that it is less for grade 4. Note also that the incidence of lack of improvement or of no change is greatest among patients classified as having grade 4 disease. These findings would indicate that the results of treatment are obviously dependent on the degree of vascular sclerosis present. First column signifies considerable improvement, second column slight improvement, third column no change and fourth column worse.

27, or 44 per cent) and about one third of the patients with grade 3 disease showed notable improvement (14 of 41, or 23 per cent). Given in the form of a chart, the data illustrate what a patient may expect when he starts using this apparatus provided acute vascular occlusions or trauma [10] does not accelerate the progress of his disease.

10. Trauma is used in the broadest sense of the word and includes not only mechanical trauma but thermal, chemical, toxic and psychic trauma as well.

COMMENT

From the start, our idea was to supply the patient suffering from advanced obliterative vascular disease with a simple inexpensive type of treatment which could be used at home for a long time without interfering with his work. It is true that absolute rest in a hospital, preferably on an oscillating bed, is superior to any type of conservative management. On our service this treatment is reserved for patients in a pregangrenous or gangrenous state who have continuous pain at rest, with pronounced edema of the foot and ankle, and who sit up all night hanging their feet down and thereby getting some relief. Extremities can be saved by this method. The material studied here, however, is of a different nature. These are ambulatory patients with intermittent claudication, numbness and tingling of the toes, often associated with angina pectoris, who have been told in the past that nothing can be done for them but that they must simply await the unpredictable progression of an incurable disease. To the patient, this often means that gangrene will develop and that he is doomed to loose his leg since that is what he saw happen in some older members of his family. If the rhythmic constrictor did nothing else but supply the patient with a harmless placebo, it would fulfill a need in geriatric practice.

Our experience, however, with individual cases extending as long as ten years has convinced us of the definite value of this method. We are well aware of the pitfalls of evaluating the merits of any method for the treatment of peripheral vascular disease. There are factors which are difficult to control, i. e., spontaneous improvement, sudden exacerbation of the local fault, acute vascular accidents elsewhere, the effect of seasonal variations in temperature and humidity and the effect of other forms of treatment such as, for instance, abstinence from tobacco. In addition, we have lately used sympathetic ganglionectomy extensively in the treatment of both Buerger's disease and peripheral vascular sclerosis,[11] and we see no reason why patients whose vasoconstrictor tone is abolished should not get additional benefit from intermittent venous hyperemia.[1] In fact, we routinely use this method for patients who have undergone sympathectomy.

In this series, however, we eliminated all outside factors so far as possible. There were no patients with thromboangiitis obliterans included and the patients with arteriosclerosis had either stopped smoking before treatment or were permitted to smoke in moderation. "Theocalcin" (mixture of calcium theobromine and calcium salicylate) or aminophyl-

11. de Takats, G., and Evoy, M. H.: Sympathectomy for Peripheral Vascular Sclerosis, J. A. M. A. **133**:441 (Feb. 15) 1947.

line was routinely given to all patients for their coronary circulation,[12] but we have no evidence that there is any decided peripheral effect unless theobromine is given intravenously, and then it is of an evanescent nature.[13]

There is considerable controversy as to the mechanism whereby intermittent venous compression acts[14]; we have not concerned ourselves in this clinical paper with such considerations. However, our original contention that in addition to a small reactive hyperemia a mechanical filling and stretching of the terminal vascular bed takes place must be obvious to anyone who watches a foot under treatment. This may be undesirable in certain forms of arteriolar disease with venocapillary congestion and stasis, and such a situation contraindicates this treatment.

Observations, then, relating to temperature of the skin, rapidity of blood flow and circulation times before and after a single treatment cannot measure the true value of intermittent venous hyperemia. Clinical observations on controlled material extending over a period of one to several years have been recorded here; they encouraged us to continue this form of therapy as an adjuvant to surgical methods.

## SUMMARY

A series of 100 patients have been studied who have received treatment with intermittent venous hyperemia for several months or years exclusive of all other methods of treatment.

The data have been analyzed in regard to severity of the disease and duration of treatment. With less severe vascular obliteration and with longer periods of treatment, the results improved.

Improvement was measured by objective methods of which the most sensitive was found to be venous filling time and walking ability.

Diabetic patients with involvement of the peripheral nerves, patients with pronounced vascular spasm and those with arteriolar and capillary stasis are not suitable subjects. Patients with vascular sclerosis in whom the preliminary tests show poor response to sympathectomy or those who have already undergone sympathectomy but still have considerable claudication constitute the group for whom this form of treatment is indicated. It is intended for ambulatory patients, to be used in the home for a period of at least one year with the object of arresting or slowing down a progressive peripheral vascular sclerosis.

12. Gilbert, N. C., and Kerr, J. A.: Clinical Results in the Treatment of Angina Pectoris with the Purine-Base Diuretics, J. A. M. A. **92**:201 (Jan. 19) 1929.

13. Beck, W. C., and de Takats, G.: The Use of Sodium Nitrate for Testing the Flexibility of the Peripheral Vascular Bed, Am. Heart J. **15**:158, 1938.

14. Friedland, L. K.; Hunt, J. S., and Wilkins, R. W.: Effects of Changes in Venous Pressure upon Blood Flow in the Limbs, Am. Heart J. **25**:631, 1943.

# PANCREATIC CALCIFICATION

## Study of Clinical and Roentgenologic Data on Thirty-Nine Cases

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BY THE TERM "pancreatic calcification" we refer to calcareous deposits in the pancreas, either within the ducts or in the parenchymatous tissue outside the ducts or in both. From a practical clinical standpoint the inclusive term "pancreatic calcification" seems preferable to the term "calculi." Accordingly, we have refrained from using the word "calculi" in order to avoid the possible implication that calcific deposits are necessarily located within the ducts.

Pancreatic calcification was apparently first reported by Graaf [1] in 1667. Haggard and Kirtley [2] in 1939 reviewed the incidence for a period of two hundred and seventy-one years and could find authentic records of only 204 cases. Mayo [2a] reported on 25 proved cases of pancreatic calculi at the Mayo Clinic prior to 1936. That this complication of pancreatic disease is being recognized with increasing frequency is evidenced by the fact that prior to 1925 only 102 cases were reported whereas from 1925 to 1942 inclusive 118 cases were reported in the literature.[3] Snell and Comfort [4] have also pointed out the fact that pancreatic calcification is being recognized with increased frequency.

### OBJECTIVES AND PLAN OF STUDY

The objectives of the present analysis were (1) to study the symptomatology and the roentgenologic features in cases of pancreatic calcification and (2) to learn whether there is any correlation between the extent of calcification in the pancreas and the incidence of clinical

1. Graaf, cited by Haggard and Kirtley.[2]

2. Haggard, W. D., and Kirtley, J. A., Jr.: Pancreatic Calculi: A Review of Sixty-Five Operative and One Hundred and Thirty-Nine Nonoperative Cases, Ann. Surg. **109**:809-824 (May) 1939.

2a. Mayo, J. G.: Pancreatic Calculi, Proc. Staff Meet., Mayo Clin. **11**:456-457, 1936.

3. Jaleski, T. C.: Pancreatic Lithiasis, Ann. Int. Med. **20**:940-947 (June) 1944.

4. Snell, A. M., and Comfort, M. W.: The Incidence and Diagnosis of Pancreatic Lithiasis: Review of Eighteen Cases, Am. J. Digest. Dis. **8**:237-243 (July) 1941.

manifestations, with particular reference to the manifestations of other complications of pancreatic disease such as diabetes mellitus and steatorrhea.

Evidence of pancreatic calcification is primarily a matter of roentgenologic diagnosis in the absence of surgical or postmortem examination of the pancreas since there are no symptoms or signs by which calcification can be diagnosed. In view of this fact, we studied the roentgenologic and clinical features of patients who on roentgenologic examination were found at the Mayo Clinic in the years 1939 to 1943 inclusive to have pancreatic calcification.

## ANALYSIS OF DATA

*Relation Between Calcification and Pancreatitis.*—There were 39 cases in which, in the opinion of one of us (D. G. P.), the criteria for the roentgenologic diagnosis of pancreatic calcification were fulfilled.

TABLE 1.—*Incidence of Pancreatitis in Thirty-Nine Cases of Pancreatic Calcification*

| Group | Pancreatitis | Cases | |
|---|---|---|---|
| | | Number | Percentage |
| 1 | Proved | 22 | 56 |
| 2 | Probable | 4 | 10 |
| 3 | Possible | 8 | 21 |
| 4 | Negative history | 5 | 13 |

When the records of these cases were studied it was found that with reference to the diagnosis of pancreatitis the patients could be conveniently divided into four groups, namely, (1) those who had proved pancreatitis, (2) those who had probable but unproved pancreatitis, (3) those who had possible pancreatitis and (4) those who had no symptoms at any time which were in any way suggestive of pancreatitis (table 1).

Although the criteria which were used for the diagnosis of pancreatitis in this series of cases have been described in previous reports,[5] a brief summary of them is indicated at this point. A diagnosis of relapsing pancreatitis is justifiable in the presence of recurrent severe attacks of pain in the upper part of the abdomen commonly lasting for hours or days and often requiring the administration of more than one hypodermic injection of opiate, provided other causes for such attacks

5. (*a*) Comfort, M. W.; Gambill, E. E., and Baggenstoss, A. H.: Chronic Relapsing Pancreatitis: A Study of Twenty-Nine Cases Without Associated Disease of the Biliary or Gastro-Intestinal Tract, Gastroenterology **6**:239-285 (April); 376-408 (May) 1946. (*b*) Gambill, E. E.; Comfort, M. W., and Baggenstoss, A. H.: Unpublished data.

have been excluded and there is evidence of one or more of the following: (*a*) steatorrhea not otherwise explained, (*b*) pancreatic calcification on roentgenologic examination or on surgical exploration or at necropsy, (*c*) supernormal concentration of amylase or lipase in the blood serum, (*d*) an enlarged, hard, nodular, edematous pancreas observed at surgical exploration and (*e*) leukocytic infiltration, interstitial fibrosis, residual necrosis, atrophy, calcification, pseudocysts and abscess formation in pancreatic tissue obtained for biopsy or at necropsy. Although pain is often severe and prolonged, it is not always so; in some instances it may be relatively mild and atypical.

In this series group 1 was made up of 22 cases, or 56 per cent of the total. In 19 of these the diagnosis of pancreatitis was proved by the findings at operation or necropsy. In the 3 remaining cases of this group the criteria for the diagnosis of pancreatitis which were summarized in the preceding paragraph were satisfied.

Group 2 consisted of 4 cases, or 10 per cent of the total, and included those in which the patients had probable but not proved pancreatitis. In these cases there was a history of recurrent attacks of severe pain in the upper part of the abdomen which required opiates for relief and were suggestive of pancreatitis. Roentgenographic study of the gallbladder, stomach and duodenum had failed to disclose in these organs evidence of disease sufficient to explain the pain.

Group 3, which consisted of 8 cases, or 21 per cent of the total, included those in which the history was compatible with that obtained in the usual case of pancreatitis but was not typical. In 4 of the 8 cases there was a history of acute severe pain in the upper part of the abdomen, but the details were too poorly remembered to be of much clinical value. In the remaining 4 cases of this group there were complaints of pain in the upper part of the abdomen which were related particularly to alimentation but were not suggestive of pancreatitis. Flatulent dyspepsia and at times anorexia and nausea were experienced.

Group 4, which was composed of 5 cases, or 13 per cent of the total, comprised those in which no history suggestive of pancreatitis was given. One patient complained of mild pain and soreness in the right upper part of the abdomen which were relieved by lying down or by sitting. None of the other 4 patients of this group gave any history of abdominal pain. Gaseous dyspepsia and constipation were noted by 2 patients. One must keep in mind the possibility that the patients in this group could have had one or more relatively mild, unremembered episodes of acute pancreatitis in early life. Another possibility is that calcium had been deposited in the pancreas of these persons in response to a low grade, subclinical pancreatitis in a manner analogous to that of the deposition of calcium in the lung or lymph nodes in tuberculosis.

It would appear from these findings that pancreatic calcification is usually associated with a history of pancreatitis but not necessarily always.

*Sex.*—Of the 39 patients, 28, or 72 per cent, were males and 11 were females, a ratio of 2.5 : 1.0. The predominance of males over females has been observed also in chronic pancreatitis, in which a ratio of 4.3 : 1.0 was noted in 56 cases.[5]

*Age.*—In the 39 cases of pancreatic calcification the median age at the time that calcification was first discovered was 43 years; the youngest age was 10 years and the oldest 70 years.

In 21 of the 22 cases of proved pancreatitis in which data were available the median age at which seizures first appeared was 30 years, the youngest age 10 years and the oldest age 65 years. Thus in one half of the cases the painful seizures began before the patient was 30 years old.

*Weight.*—Patients were of approximately normal weight for their height and age. Those who suffered from frequent severe episodes of pain and in whom diabetes mellitus or steatorrhea developed frequently lost between 15 and 20 per cent of their original weight.

*Painful Seizures Associated with Pancreatic Calcification.*—Precipitating Causes: The possible influence of trauma, exercise and alcohol in the precipitation of the attacks of pain of pancreatitis has been discussed in previous studies.[6] In 1 case of proved pancreatitis the first attack of pain came while the patient was playing baseball. These attacks continued to recur two to four times a year. Pancreatic calcification was discovered three years after the initial attack of pain. In another case of proved pancreatitis the patient remarked that yelling, running or lifting tended to induce the attacks of pain. In 5 of the 22 cases of proved pancreatitis the use of alcohol seemed to precipitate the attacks.

Duration and Frequency of Occurrence of Attacks of Pain: The time which had elapsed since the onset of seizures of pain varied from two months to twenty-two years, with an average of 6.6 years. The seizures lasted from one hour to three weeks. Repeated hypodermic injections of morphine were often needed to control the pain. The frequency of occurrence of seizures varied from five weekly to one every six years. The general tendency was for the attacks to become increasingly frequent, severe and prolonged with the passage of time.

6. Myers, W. K., and Keefer, C. S.: Acute Pancreatic Necrosis in Acute and Chronic Alcoholism, New England J. Med. **210**:1376-1380 (June 28) 1934. Weiner, H. A., and Tennant, R.: A Statistical Study of Acute Hemorrhagic Pancreatitis (Hemorrhagic Necrosis of Pancreas), Am. J. M. Sc. **196**:167-176 (Aug.) 1938. Footnote 5*a* and *b*.

In a few cases, however, the attacks tended to become less severe after a few years. We wish to make it clear that we regard the attacks of pain primarily as manifestations of pancreatitis rather than of calcification.

Interval Between Occurrence of First Painful Seizure and Discovery of Calcification: The time that elapsed between the occurrence of the first painful seizure and the discovery of calcification, diabetes mellitus and pancreatic steatorrhea is given in table 2. While in about one fifth of the cases calcification was noted a year after the onset of attacks of pains, in another fifth calcification was not apparent until eleven to twenty-two years after. Likewise, the intervals between the onset of severe pain and the discovery of diabetes or steatorrhea varied widely.

Relation of Site of Calcification to Site of Pain: Reasoning that pancreatic calcification is most commonly the result of previous inflam-

TABLE 2.—*Years Between Onset of Attacks of Severe Pain and the Discovery of Pancreatic Calcification, Diabetes Mellitus and Steatorrhea* *

| Years | Calcification, Number of Cases | Diabetes, Number of Cases | Steatorrhea, Number of Cases |
|---|---|---|---|
| 1 | 8 | 3 | 1 |
| 2 to 10 | 17 | 3 | 4 |
| 11 to 22 | 8 | 3 | 2 |
| Unknown | 2 | 0 | 0 |
| No pain | 4 | 0 | 0 |

* Based on 39 cases of pancreatic calcification.

mation and that pain during the attacks is due to inflammation or edema, we attempted to see if there was any association between the site of calcification in the pancreas and the primary site of pain during the acute seizures. In general it was found that when calcification was limited to the head of the pancreas the pain was usually felt first in the right upper part of the abdomen or in the epigastrium whereas when the calcification was present throughout the pancreas the pain more often than not was felt first in the epigastrium. While in some cases pain was confined to the initial or primary site, in many it was also propagated to other regions so that the entire upper region of the abdomen became involved.

*Associated Complications.*—Complications which were found in association with pancreatic calcification were diabetes mellitus, steatorrhea, gastrointestinal hemorrhage, morphinism, pancreatic pseudocyst, pancreatic abscess and peripheral neuritis (table 3).

Diabetes Mellitus and Steatorrhea: In 5 cases of the 10 in which diabetes developed the disease appeared within three years after the

onset of painful seizures. Occasionally diabetes mellitus or steatorrhea did not appear until after many years of recurrent attacks of pancreatitis. While it is doubtful whether calcification as such has much to do with the development of diabetes, proof is lacking to substantiate this doubt. The destruction of the islet tissue by repeated attacks of acute inflammation with or without necrosis would seem to be a more reasonable theory for the causation of instances of diabetes.

TABLE 3.—*Complications Associated with Pancreatic Calcification*

| Complication | Cases | |
|---|---|---|
| | Number * | Percentage * |
| Diabetes mellitus | 9 | 23 |
| Pancreatic steatorrhea | 7 | 18 |
| Gastrointestinal hemorrhage | 3 | 8 |
| Morphinism | 3 | 8 |
| Inflammatory pancreatic pseudocyst | 2 | 5 |
| Pancreatic abscess | 1 | 3 |
| Peripheral neuritis | 1 | 3 |

* Based on 39 cases of pancreatic calcification.

The incidence of diabetes or steatorrhea or of both in cases of pancreatic calcification was much greater among patients who gave a history suggestive of pancreatitis than among those who did not. As a matter of fact, in this series diabetes or steatorrhea or both occurred only in cases of calcification in which there was an associated history

TABLE 4.—*Incidence of Diabetes and Steatorrhea in the Presence of Pancreatic Calcification With and Without a History of Pancreatitis* *

| History of Pancreatitis | Pancreatic Calcification | | | | |
|---|---|---|---|---|---|
| | Cases | Diabetes | | Steatorrhea | |
| | | Cases | Percentage | Cases | Percentage |
| Positive | 22 | 9 | 41 | 7 | 32 |
| Negative or doubtful | 17 | 0 | 0 | 0 | 0 |

* Based on 39 cases of pancreatic calcification.

of pancreatitis (table 4). The evidence indicates, therefore, that when calcification is found in a case of chronic relapsing pancreatitis it is prone to be associated with serious impairment in pancreatic function indicative of advanced disease. On the contrary, pancreatic calcification which is discovered, accidentally or otherwise, in a person who gives no previous history of pancreatitis or a questionable one is generally not prone to be associated with any gross disturbances in pancreatic function.

As might be anticipated, there seemed to be a high degree of positive correlation between the extent of calcification in the pancreas and the

incidence of diabetes and steatorrhea. Thus in 23 cases in which the calcification was limited to the head of the pancreas only 4 instances of diabetes or steatorrhea occurred, whereas in 11 cases in which calcification involved the entire pancreas there were 9 instances of diabetes or steatorrhea.

It should be emphasized, however, that extensive pancreatic calcification is not always associated with signs of pancreatic insufficiency, as is illustrated by 1 case (fig. 1). The patient suffered from one attack of pain suggestive of gallstone colic ten years before admission to the

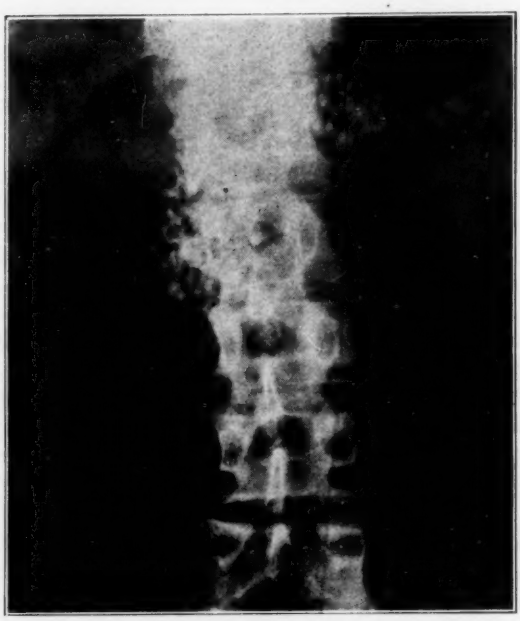

Fig. 1.—Possible pancreatitis. There is extensive calcification throughout the pancreas.

clinic. There had been no indigestion for seven years prior to admission. The cholecystogram did not reveal disease of the gallbladder but demonstrated pancreatic calcification. There were no symptoms or signs of pancreatic insufficiency; however, no tests were performed to detect any possible subclinical deficiency.

There appeared to be no positive correlation between the size, shape or method of grouping of the calcareous deposits and the degree of pancreatic insufficiency. Moreover, the extent of calcification and the degree of disturbance of pancreatic function were not necessarily related

to the length of time during which a patient had been suffering from the severe seizures of pain.

Gross Gastrointestinal Hemorrhage: Gross bleeding from the upper part of the gastrointestinal tract in the absence of demonstrable peptic ulceration or of other gross lesions of the esophagus, stomach, duodenum or liver has been observed in patients who have pancreatitis. Because of the frequent occurrence of the factor of alcoholism, it has been suspected that such bleeding may possibly be due to alcoholic gastritis.[5] In this series of 39 cases of calcification 3 patients had a history of gross hemorrhages from the upper part of the gastrointestinal tract. One patient suffered from recurrent gross hematemesis. He used alcohol chronically. Physical, roentgenographic and gastroscopic examinations were noncontributory. At exploration the surgeon found chronic pancreatitis but no evidence of any lesion of the stomach or duodenum.

Another patient suffered from recurrent hematemesis and melena. He likewise was a heavy user of alcohol. Roentgenograms of the stomach and duodenum did not reveal any disease. At exploration the surgeon found severe chronic pancreatitis, with pancreatic pseudocyst and abscess in the lesser peritoneal sac, but no gross lesions of the stomach or duodenum.

The third patient, who had severe chronic pancreatitis with diabetes and steatorrhea, had become addicted to the use of alcohol and morphine. While residing in a hospital in an effort to get rid of the addiction to opiates, he experienced a gastrointestinal hemorrhage which was fatal. Necropsy revealed that a spicule of calcium in the head of the pancreas had apparently eroded through the duodenum, thus causing the fatal hemorrhage.

Morphinism: While morphinism is not strictly a complication specific for pancreatitis, it may result from the use of morphine for relief of the frequent exacerbations of severe pain. Consequently it may be difficult for the clinician to assess how much of the syndrome is due to results of addiction to morphine and how much to pancreatitis. In this series of 39 cases of pancreatic calcification there were definitely 2 and probably 3 patients who were addicted to opiates. Two of these patients had to go to an institution because of such addiction, which had been induced by the use of opiates for relief of the frequent and severe attacks of pancreatitis.

Pancreatic Pseudocysts: In this series of cases two pseudocysts occurred. They appeared to be the result of acute pancreatitis with necrosis and not secondary to calcareous deposits within the ducts.

Pancreatic Abscess: In 1 case of this series two abscesses were observed in the tail of the pancreas at necropsy. These were the result

of acute pancreatitis with necrosis. In another case an abscess developed in the lesser peritoneal sac as a result of acute pancreatitis with necrosis.

Peripheral Neuritis: Peripheral neuritis developed in 1 patient who also had pancreatic calcification, diabetes mellitus and steatorrhea as complications of chronic pancreatitis. The exact etiologic basis for the neuritis in this case was not clear, although it appeared to be largely the result of severe malnutrition and diabetes.

*Roentgenographic Aspects.*—Calcareous deposits in the pancreas are almost always rather dense and therefore radiopaque. For this reason the roentgenologic diagnosis can be made with accuracy,[7] and the clinical diagnosis is dependent on this fact. In many instances it is the repeated painful seizures that eventually lead to the suspicion of pancreatitis and to the discovery of pancreatic calcification. Frequently the clinician may suspect the presence of gallstones and may make a cholecystogram only to find a normally functioning gallbladder and calcification in the pancreas. Occasionally pancreatic calcification is accidentally discovered at the time of roentgenologic study of the stomach, duodenum or colon. Roentgenographic study of the kidneys or of the lumbar vertebrae may commonly disclose the presence of unsuspected pancreatic calcification. It is in the group with unsuspected disease that the diagnosis of calcification is most important, since such a diagnosis may direct attention to pancreatic disease that might otherwise remain unrecognized.

Any roentgenograms that include all or part of the pancreatic region may reveal calcareous deposits. In this series the deposits were seen most frequently, perhaps, in cholecystograms (fig. 2) or in localized roentgenograms of the gallbladder region (fig. 3). They were also discovered during roentgenologic examination of the gastrointestinal tract. In some instances roentgenograms of the abdomen or of the urinary tract revealed their presence (figs. 4 and 5). In roentgenograms of the lumbar vertebrae they were seen not only with the anteroposterior projection but also with the lateral and oblique views (fig. 5). If the presence of pancreatic calcareous deposits is suspected, localized anteroposterior, oblique and lateral roentgenograms of the area centered around the first and second lumbar vertebrae are most helpful. The pancreas varies somewhat in its location depending on the patient's habitus, but in this series calcareous shadows were seen most frequently at the level of the first and second lumbar vertebrae. At times

7. Case, J. T.: Roentgenology of Pancreatic Disease: Caldwell Lecture, 1939, Am. J. Roentgenol. **44**:485-518 (Oct.) 1940. Gillies, C. L.: Pancreatic Lithiasis, with Report of a Case, Am. J. Roentgenol. **41**:42-46 (Jan.) 1939. McCullough, J. A. L., and Sutherland, C. G.: Intra-Abdominal Calcification: Interpretation of Its Roentgenologic Manifestations, Radiology **36**:450-457 (April) 1941.

Fig. 2.—Possible pancreatitis. There are irregular dense calcareous deposits in the head of the pancreas and a normally functioning gallbladder.

**Fig. 3.—Proved pancreatitis. Calcification is present in the head of the pancreas and in part of the body.**

they were seen as high as the level of the eleventh thoracic vertebra or as low as the level of the third lumbar vertebra. Calcification was present in various sites in the pancreas, but it was seen most frequently in the head just to the right of the spinal column (figs. 2 and 3). At times calcification was situated in the head or body of the pancreas

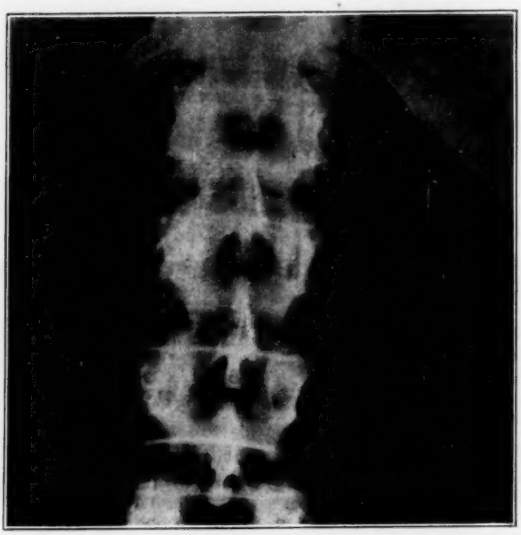

Fig. 4.—Proved pancreatitis. Calcification is present throughout the pancreas.

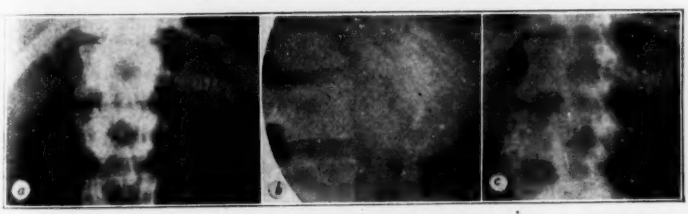

Fig. 5.—Proved pancreatitis. *a*, extensive calcification, especially in the tail of the pancreas; *b*, lateral view; *c*, oblique view.

overlying the vertebrae, and thus calcific shadows were occasionally difficult to see. Oblique and lateral roentgenograms were of assistance in such instances (fig. 5). It is important that the roentgenograms cover the entire pancreatic region since otherwise small localized shadows of calcification, particularly if situated in the tail of the pancreas, may be missed. In a few cases there was extensive calcification throughout the

gland from head to tail, and in such cases the shape of the pancreas was well shown in the roentgenograms (figs. 1, 4 and 6).

Deposits of calcium in the pancreas varied greatly in shape and size (fig. 3). In some cases they were tiny, being only a few millimeters in diameter. Numerous small calcific shadows of this type were usually present when there was extensive involvement of the entire gland. Larger, well circumscribed deposits were encountered; these occurred most commonly in the head or body of the pancreas. Shadows of calcification were sometimes seen which had the appearance of irregular, conglomerate masses of calcium. In rare instances extremely large calcareous shadows, at times several centimeters in diameter, were seen. The finding of facetted stones in the duct of Wirsung has been reported, but this is extremely unusual. Calcareous deposits of different shapes and sizes were often seen in the same gland.

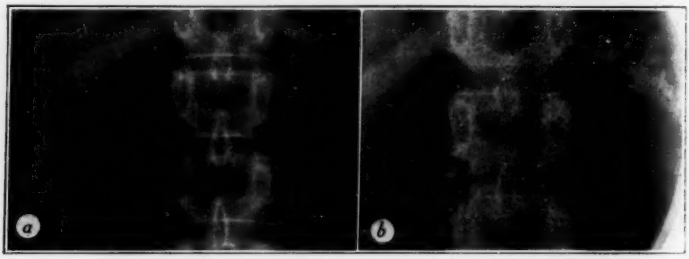


Fig. 6.—Proved pancreatitis. *a*, cholecystogram in 1935 revealed no pancreatic calcification and a functioning gallbladder; *b*, calcification throughout the pancreas in 1940.

In some instances the roentgenologic diagnosis of pancreatic calcification can be made with ease because of the location, size, shape and density of the calcareous deposits. However, other conditions which produce calcific shadows in the upper part of the abdomen must be differentiated from pancreatic calcification. Gallstones are frequently facetted, are more laterally situated and are not often so densely calcified as are calcific deposits in the pancreas. Occasionally in the cholecystogram the gallbladder appears to overlie the vertebrae; it is possible that gallstones in a gallbladder located in that position might resemble calcareous deposits in the pancreas. Stones in the common bile duct could be difficult to distinguish from calcific shadows in the pancreas, but the former are seldom densely calcified. Renal calculi are seen somewhat lateral to the pancreatic region. It is conceivable that renal calculi in a horseshoe kidney could be mistaken for pancreatic calcification. Calcified mesenteric nodes in the region of the head of the pancreas may be difficult to distinguish from calcification within the

pancreas, but as a rule the so-called mulberry appearance of calcified nodes and their presence in other parts of the abdomen make possible the correct diagnosis. Calcification of the suprarenal gland can usually be identified by its location and shape.

Calcification of the abdominal aorta is linear and can be easily identified in the lateral view. Calcification of the arteries of the celiac axis is seen as linear, crescentic or annular shadows of calcification. Localized calcification of the vertebral ligaments or calcification of the nucleus pulposus may be seen at the level of the head of the pancreas, but these should cause no confusion. At times special examinations, such as cholecystography and excretory urography, are necessary before a definite diagnosis can be made. Roentgenologic study after the stomach and duodenum have been filled with barium will aid in showing the relationship of calcareous shadows to the pancreatic region. However, special studies of this type are seldom necessary.

*Treatment.*—The indications for treatment of pancreatic calcification are primarily those employed for the treatment of pancreatitis, which we believe is the most common precursor of calcification.

Medical treatment seems to have little effect in preventing the painful exacerbations or in arresting the progress of the disease. A bland diet relatively low in fat, the abstinence from alcoholic excesses and the avoidance of excessive nervous and physical stress were advised, but there was no real evidence that these measures had any effect in reducing the frequency of occurrence or the severity of painful seizures. Whenever indicated, insulin was employed for diabetes mellitus and pancreatin for pancreatic steatorrhea. The diabetes was relatively mild. In instances of steatorrhea it was noted that the amount of fat lost in the feces could be materially reduced by the use of pancreatin in appropriate amounts, usually from 2 to 10 Gm. three times a day. There were 9 cases of diabetes mellitus and 7 cases of steatorrhea. In 21 of the 39 cases operation was not performed.

For those who are afflicted with frequent attacks of severe pain surgical intervention is the treatment of choice, although it is not always effective in stopping the attacks of pain and the results in a given case are unpredictable. Surgical intervention was carried out in 18 of the 39 cases of this series for one or more of the following reasons: (1) to arrest the progress of the disease or at least to try to reduce or abolish the frequency of occurrence and the severity of the painful seizures, (2) to relieve obstruction of the duodenum or of the common bile duct due to an enlarged pancreas, (3) to remove calcareous masses which might possibly be obstructing the exit of the main pancreatic duct and (4) to drain or remove pseudocysts or abscesses of the pancreas. While any type of treatment may give discouraging

results and while the effectiveness of any given treatment is unpredictable, about two fifths of the patients who suffered from recurrent attacks of pain were completely relieved and about one fifth were partially relieved of the acute seizures for significant periods after certain surgical procedures designed to promote prolonged internal or external drainage of the common bile duct had been carried out. These procedures were cholecystogastrostomy, cholecystojejunostomy, choledochoduodenostomy and external drainage of the common bile duct by means of a T tube for at least six to twelve months. Of these, we are inclined to favor prolonged T tube drainage or, preferably, choledochoduodenostomy when that operation is feasible.

Pancreatolithotomy was performed on 1 patient; the surgeon removed some calcareous masses in and around the exit of the major pancreatic ducts. This procedure followed by roentgen therapy applied over the pancreatic region resulted in cessation of the painful seizures. Partial or total pancreatectomy was not employed in any of the cases of this series. We doubt that such procedures are justifiable except for patients who have severe and irreparable pancreatic insufficiency and who are invalided by intractable pain.

*End Results.*—No immediate surgical deaths occurred among the 18 cases in which operation was performed. One patient died, approximately three years after leaving the clinic, of a subhepatic abscess, which was thought to be secondary to leakage at the site of cholecystogastrostomy, which had been done previously for pancreatitis. Another patient, who had not had surgical treatment, died a month after leaving the clinic. Necropsy was reported to show chronic pancreatitis with calcification, two abscesses in the pancreas and acute vegetative endocarditis. A third patient died of a massive gastrointestinal hemorrhage as the result of erosion through the wall of the duodenum by a spicule of calcium in the pancreas.

In a few cases spontaneous amelioration of the painful seizures occurred, and in others the disease progressed in spite of all efforts by the clinician and the surgeon. In still others the severity of the disease did not change. Some patients became almost incapacitated for work, undernourished and addicted to opiates. Others turned to alcohol for spurious relief of what seemed to be a hopeless plight. The necessity for frequent hospitalization, numerous surgical operations and payment of medical bills and the inability to work constituted a serious economic, mental and emotional strain which sapped the morale of some of the patients.

## SUMMARY

In a study of 39 cases of pancreatic calcification, selected solely on the basis of roentgenologic evidence of calcification, it was found that

calcareous deposits in the pancreas were usually but not always associated with relapsing pancreatitis. Commonly the symptomatology was that of pancreatitis, although in approximately two fifths of the cases there was either no history of pancreatitis or a doubtful one. Among cases in which a definite history of pancreatitis was obtained, calcification became evident in a fifth in one year after the onset of pain, but in another fifth calcification was not discovered until after eleven to twenty-two years.

Associated complications in the order of frequency of occurrence were diabetes, steatorrhea, gastrointestinal hemorrhage, morphinism, pancreatic pseudocyst, pancreatic abscess and peripheral neuritis.

There was a high degree of positive correlation between the extent of pancreatic calcification and the incidence of two other complications associated with pancreatic calcification, namely, diabetes and steatorrhea. Diabetes and steatorrhea occurred only in cases of calcification in which there was a definite diagnosis of pancreatitis.

# INSULIN ALLERGY

## Treatment With the Histamine Antagonists

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### INCIDENCE OF INSULIN ALLERGY

INSULIN allergy, the antigenic response to the insulin protein, is a rare but important occurrence in diabetic management. The incidence of allergic reactions to insulin varies widely in the reports in the literature. Some observers considered mild local reactions as allergic manifestations. Others were found to exclude all local reactions regardless of severity and to designate as allergic only those patients for whom insulin therapy had to be discontinued. Hence such wide variations as Grafe's [1] 0.15 per cent, Collens' [2] 7.3 per cent and Allan and Scherer's [3] 11.7 per cent were reported. Of persons sensitive to insulin, Allan and Scherer estimate that from 98 to 99 per cent will show a reaction limited to the site of injection while only 1 or 2 per cent will exhibit general or systemic manifestations. Thus, approximately one in a thousand using insulin will have a generalized reaction.

Mild local reactions usually disappear within two weeks of the onset of therapy. These reactions are believed to be due to extraneous material within the preparation and not to the insulin itself. A change in the brand of insulin is frequently all that is necessary to do away with this reaction.

Insulin allergy causes a local reaction of increasing severity. A generalized urticaria accompanied with severe pruritus appears. Other common manifestations are angioneurotic edema, arthralgia, gastrointestinal symptoms, bronchial asthma and circulatory failure. Less frequently generalized erythemas, pruritus without urticaria and eruptions

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1. Grafe, E.: Probleme der Insulintherapie, München. med. Wchnschr. **83**: 1255-1258, 1936.

2. Collens, W. S.; Lerner, G., and Fialka, S. M.: Insulin Allergy: Treatment with Histamin, Am. J. M. Sc. **188**:528-533, 1934.

3. Allan, F. N., and Scherer, I. R.: Insulin Allergy, Endocrinology **16**: 417-430, 1932.

of a morbilliform, scarlatiniform or vesicular type are seen. Occasionally insensitivity to the antidiabetic activity of insulin is demonstrated.

Allan and Scherer [3] reported their experiences with 100 cases of insulin allergy observed at the Mayo Clinic. Of the 100 patients, 84 showed a mild local reaction. This was usually seen between the third and fourteenth days of therapy. In 12 instances there were severe local reactions lasting one or more weeks. In only 4 cases were generalized reactions seen; these consisted of cutaneous, circulatory and gastrointestinal symptoms.

## INSULIN IS A PROTEIN

That the crystalline pure hormone insulin is a protein is definitely established. Abel [4] described the preparation of pure crystalline insulin and found that its chemical reactions were characteristic of protein substances. Examining the crystalline insulin derived from the pancreas of various animals (ox, sheep, hog and fish), he found them to have similar microscopic appearances, solubilities, isoelectric points and carbon, hydrogen, nitrogen and sulfur content. Jensen,[5] in chemical studies of insulin, was able to derive numerous amino acids from it and also found that its reactions were characteristic of protein substances.

## ANTIGENIC ACTIVITY OF INSULIN

The antigenic activity of insulin has been demonstrated experimentally by various workers. Barral and Roux [6] found that the sensitization following the injection of insulin is specific for the hormone itself and is not related to that produced by proteins of beef serum or beef pancreas. Wassermann and others [7] demonstrated that insulin is antigenic. Serums from sensitized rabbits gave positive reactions to complement fixation tests. Bernstein, Kirsner and Turner [8] have shown that guinea pigs given parenteral injections with commercial and crystalline insulin reacted with anaphylaxis to subsequent intravenous injections. Raynaud and Lacroix [9] were able to demonstrate the presence of precipitins in the blood serum of an allergic patient. They were also able to sensitize a guinea pig with insulin and then produce ana-

4. Abel, J. J.: Crystalline Insulin, Proc. Nat. Acad. Sc. **12**:132-136, 1926.

5. Jensen, H.: Chemical Study of Insulin, Science **75**:614-618, 1932.

6. Barral, P., and Roux, J.: L'insuline constitute-t-elle en elle-même un antigène spécifique? Compt. rend. Soc. de biol. **106**:292-293, 1931.

7. Wassermann, P.; Broh-Kahn, R. H., and Mirsky, I. A.: Antigenic Property of Insulin, J. Immunol. **38**:213-219, 1940.

8. Bernstein, C., Jr.; Kirsner, J. B., and Turner, W. J.: Studies on Anaphylaxis with Insulin, J. Lab. & Clin. Med. **23**:938-944, 1938.

9. Raynaud, A., and Lacroix, A.: Anaphylactic Shock from Insulin: Pathogenesis of Insulin Edema, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:831, 1925

phylactic shock by injection of the blood serum of an allergic patient. Lewis,[10] using the Schultz-Dale uterine muscle technic to study the antigenic properties of insulin, found that the muscle strips sensitized to beef insulin did not react in the presence of beef pancreas or beef serum but did react to beef insulin. Cross reactions were obtained between beef and pork insulin.

### IMPORTANCE OF INSULIN ALLERGY

No fatal immediate reactions following the use of insulin have been reported. However, several deaths have been attributed indirectly to insulin allergy.

Goldner and Ricketts[11] reported a case in which insulin allergy acted as a contributory cause of death. The patient, who had mild diabetes, was allowed to go untreated. Subsequent bronchopneumonia precipitated severe acidosis. Efficient antidiabetic therapy could not be instituted, and death resulted. Lereboullet[12] treated a 4 year old diabetic child who at first responded well to insulin. She was given measles convalescent serum and diphtheria prophylaxis. Subsequently, each injection of insulin was followed by urticaria and by generalized edema. The symptoms abated when administration of insulin was stopped, but they recurred even with a change of brand. When measles developed, diabetic coma followed. Attempted desensitization resulted in general urticaria and edema. Insulin allergy was a factor in the fatal outcome.

Failure to respond to insulin may be the result of insulin allergy. Thus, Glassberg and others[13] described a patient who was resistant to insulin therapy and required 300 units daily. Injections of insulin from various animal sources resulted in severe local reactions. Desensitization with insulin was followed by gradual diminution in the refractoriness. Karr, Scull and Petty[14] reported the development of extensive local induration following injections of insulin, accompanied with severe insulin refractoriness. After the subsidence of the reaction, the amount of insulin required was markedly reduced. Foerster[15] reported on a patient who used insulin with benefit and then discontinued using it. When therapy was commenced once more, the insulin

10. Lewis, J. H.: Antigenic Properties of Insulin, J. A. M. A. **108**:1336-1338 (April 17) 1937.

11. Goldner, M. G., and Ricketts, H. T.: Insulin Allergy: Report of Eight Cases with General Symptoms, J. Clin. Endocrinol. **2**:595-602, 1942.

12. Lereboullet, P.; Lelong, M., and Frossard, R.: Eruptions Under Insulin Treatment, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:1184-1190, 1924.

13. Glassberg, B. Y.; Somogyi, M., and Taussig, A. E.: Diabetes Mellitus: Report of Case Refractory to Insulin, Arch. Int. Med. **40**:676-685 (Nov.) 1927.

14. Karr, W. G.; Scull, C. W., and Petty, O. H.: Insulin Resistance and Sensitivity, J. Lab. & Clin. Med. **18**:1203-1211, 1933.

15. Foerster, E.: Paradoxic Action of Insulin, Med. Klin. **22**:846-849, 1926.

proved ineffective, and considerable glycosuria and acetonuria were observed. Generalized urticaria occurred. Insulin in large doses failed to bring about the anticipated effect. Foerster expressed the belief that the insulin allergy interfered in some way with the action of the insulin hormone. Grote's [16] patient showed an increasing tolerance to insulin. After a period of latency there was a sudden urticarial attack. When the usual dose of insulin was given, hyperglycemia, glycosuria and ketosis developed. More insulin was required for control.

Insulin refractoriness is not a constant accompaniment of insulin allergy. Allen and Scherer [3] as well as Herzstein and Pollack [17] reported no change in the physiologic action of insulin in their cases.

### TREATMENT OF INSULIN ALLERGY

Many of the local reactions following the injection of insulin are not allergic. Thus, with the removal of impurities which were present in earlier products fewer reactions occurred. Alcohol used in the sterilization of the syringe and the formaldehyde in the cleansing alcohol have been incriminated.

Injection of the insulin deeply into the subcutaneous tissue, the changing of the brand of insulin to one derived from another animal source, or the employment of crystalline insulin are all effective means of combating reactions except when insulin allergy exists.

In the specific management of insulin allergy, varying degrees of success have been reported with desensitization. Methods are described by Allan and Scherer,[3] Bayer [18] and Corcoran [19] for rapid desensitization. Slow desensitization is reported by Bryce [20] and by Herold.[21]

Nonspecific measures, too, have been used in an attempt to control insulin allergy. Hunscheidt [22] suggested injection of calcium with the insulin. Strasser [23] administered calcium prior to the insulin. Collens [2] reported on the use of histamine three times weekly in gradually increas-

16. Grote, I. R.: Neuzeitliche Diabetesbehandlung, Ergebn. d. ges. Med. **18**: 301-458, 1933.

17. Herzstein, J., and Pollack, H.: Insulin Allergy: Case Report with Review of Literature, J. Mt. Sinai Hosp. **6**:3-17, 1939.

18. Bayer, L. M.: Desensitization to Insulin Allergy, J. A. M. A. **102**:1934-1936 (June 9) 1934.

19. Corcoran, A. C.: Note on Rapid Desensitization in Case of Hypersensitiveness to Insulin, Am. J. M. Sc. **196**:359-361, 1938.

20. Bryce, L. M.: Hypersensitiveness to Insulin, M. J. Australia **1**:371-376, 1933.

21. Herold, A. A.: Insulin Allergy: Report of Severe Case with Successful Desensitization, New Orleans M. & S. J. **91**:163-166, 1938.

22. Hunscheidt, H.: Calcium bei Insulinüberempfindlichkeit, Zentralbl. f. inn. Med. **55**:369-371, 1934.

23. Strasser, A.: Insulinbehandlung unter Kalkaufladung, Med. Klin. **27**: 695, 1931.

ing doses. Roth [24] reported good results in the elimination of local reactions to insulin by the daily oral administration of histaminase. Karr [14] suggested sensitization of a rabbit with the serum of the patient allergic to insulin. The rabbit's serum was then used in an attempt to desensitize the patient.

Recently Gastineau and Leavitt [25] reported the use of "benadryl hydrochloride" in the treatment of a case of insulin allergy. The patient presented local as well as generalized lesions. "Benadryl administered orally afforded almost complete relief of local and generalized urticaria, while a dilute solution of benadryl mixed with insulin prevented local reactions."

### THE HISTAMINE ANTAGONISTS

The histamine antagonists present new hope for the control of allergic manifestations. In 1937 Edlbacher, Jucker and Bauer [26] demonstrated the action of the amino acids histidine, cysteine and arginine in inhibiting the histamine-stimulated contraction of the guinea pig intestine. Landau and Gay [27] found the toxicity of these substances high and their efficacy low.

Fourneau,[28] working in France as early as 1910, prepared phenolic ethers of amino alcohols and later demonstrated their antihistamine reaction. Halpern [29] in 1942 prepared a series of related compounds. One of these substances, "antergan," and, more recently, "neoantergan" have received enthusiastic support in the French literature.

In this country investigative work for the production of efficacious antihistaminic drugs has resulted in tripelennamine hydrochloride, or "pyribenzamine hydrochloride" (N. N. R.), diphenhydramine hydrochloride, or "benadryl hydrochloride" (N. N. R.). Structural for-

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24. Roth, G. M., and Horton, B. T.: Histaminase: Physiologic Effects on Man and Its Therapeutic Value in Medicine, Bull. New York Acad. Med. **16**: 570-584, 1940.

25. Gastineau, C. F., and Leavitt, M. D.: Treatment of Allergy to Insulin with Benadryl: Report of One Case, Proc. Staff Meet., Mayo Clin. **21**:316-319, 1946.

26. Edlbacher, S.; Jucker, P., and Bauer, H.: Die Beeinflussung der Darmreaktion des Histamins durch Aminosäuren, Ztschr. f. physiol. Chem. **247**:63, 1937.

27. Landau, S. W., and Gay, L. N.: Influence of Certain Amino Acids on Histamine Reactions and Anaphylactic Reactions in Intestinal Strips of Guinea Pigs and in Intact Guinea Pigs, Bull. Johns Hopkins Hosp. **74**:55-76, 1944.

28. Fourneau, E., and Bovet, D.: Recherches sur l'action sympathicolytique d'un nouveau dérivé du dioxane, Arch. internat. de pharmacodyn. et de thérap. **46**:178-191, 1933.

29. Halpern, B. N.: Etude expérimentale des antihistaminiques de synthèse; essais de chemiothérapie des états allergiques, J. de méd. de Lyon **23**:409-411, 1942.

mulas reveal the similarity of these compounds. Tripelennamine hydrochloride differs from "antergan" only by the substitution of the pyridil ring for the phenyl and from "neoantergan" by the omission of the methoxy group.

Loew and Kaiser [30] demonstrated the value of the synthetic benzhydryl alkamine ethers in alleviating both histamine shock and anaphylactic shock in guinea pigs. Wells, Morris, Bull and Dragstedt [31] suggest that the action of these drugs is to attach themselves to some of the receptors on the cells which would ordinarily be occupied by the histamine molecules.

Recently the opportunity presented itself for the clinical trial of the antihistamine drugs in the treatment of a patient with insulin allergy.

## REPORT OF A CASE

A. B., a 46 year old housewife, was first admitted to the Boston City Hospital in April 1946. Studies revealed persistent glycosuria, acetonuria and hyperglycemia. A diet of 110 Gm. of carbohydrate, 50 Gm. of protein and 50 Gm. of fat was ineffectual in controlling her diabetes. One week after her admission to the hospital the patient was started on 10 units of protamine zinc insulin. A local reaction of moderate intensity appeared after the first injection. Each subsequent day the reaction increased in severity. Tenderness, local heat, swelling and redness were present, and they persisted for periods greater than twenty-four hours.

One week after the onset of the insulin therapy, a generalized urticarial rash appeared. The cutaneous lesions spontaneously disappeared at the end of four hours. The use of protamine zinc insulin was continued, and two days later an acute attack of nausea, vomiting and weakness was noted.

After two and one-half weeks of hospitalization the patient was discharged. She was taking 20 units of protamine zinc insulin. Local reactions at the site of the inoculation were of moderate severity.

In the following month the severity of the local reaction increased. Urticaria recurred on a number of occasions and was described as generalized and severe. Nervousness and arthralgia were noted. There were frequent episodes of nausea and vomiting. The patient discontinued taking insulin and subsequently became asymptomatic. She was advised to return to the hospital for desensitization, but because of her illness of the previous month she decided on a vacation.

In October 1946 she returned to the hospital, complaining of weakness and fatigue. The fasting blood sugar content was 235 mg. per hundred cubic centimeters, and hospitalization was once more recommended.

With the patient on a diet of 121 Gm. of carbohydrate, 53 Gm. of protein and 64 Gm. of fat, the hyperglycemia, glycosuria and acetonuria persisted. Cutaneous

30. Loew, E. R., and Kaiser, M. E.: Alleviation of Anaphylactic Shock in Guinea Pigs with Synthetic Benzhydryl Alkamine Ethers, Proc. Soc. Exper. Biol. & Med. **58**:235-237, 1945.

31. Wells, J. A.; Morris, H. C.; Bull, H. B., and Dragstedt, C. A.: Observations on Nature of Antagonism of Histamine by B-Dimethylaminoethyl Benzhydryl Ether (Benadryl), J. Pharmacol. & Exper. Therap. **85**:122-128, 1945.

tests were done, with the use of numerous brands of commercial insulin [32] (0.05 cc. containing 1 unit of insulin injected intradermally). Crystalline zinc insulin, regular insulin, globin insulin and protamine zinc insulin were used. In each instance an indurated urticarial wheal developed, surrounded by an erythematous irregular flare. The wheal persisted, although somewhat diminished, for twenty-four hours.

A dermal passive transfer test of the skin was carried out. One tenth of a cubic centimeter of the patient's serum was injected subcutaneously into the forearm of 3 normal persons. Into the other forearm a similar injection of normal serum was made. Twenty-four hours later 0.05 cc. of crystalline insulin was injected intradermally into the sensitized and nonsensitized areas. Within fifteen minutes each of the sensitized areas showed pronounced wheal and flare. This reaction continued to increase in intensity for thirty to sixty minutes and then began to fade.

Attempt to control the diabetes was made subsequently by using globin insulin and then crystalline insulin. With each product the previously described experience of severe local reaction with generalized urticaria was repeated.

It became apparent that if this patient was to receive insulin therapy it would be necessary to desensitize her or to administer concurrently a histamine antagonist. Because of the frequent failures of the former method, it was decided to use the latter.

"Benadryl hydrochloride" in a 100 mg. daily dose produced drowsiness. "Pyribenzamine hydrochloride" was substituted, and no disagreeable side reactions were noted. A dosage of 150 mg. daily was used initially. This was increased to 350 mg. A schedule of 50 mg. every three hours was found to be the most efficacious.

Protamine zinc insulin [33] (25 units administered in the morning) initially was found to produce a moderate reaction. This was neither as severe nor as persistent as the previous reactions. With the increased dosage of the antihistamine drug, the local reaction diminished. Within three days, in which time the maximum dosage of "pyribenzamine hydrochloride" was reached, the local reaction was negligible. No generalized reactions or constitutional symptoms were noted.

In order to evaluate further the effect of the "pyribenzamine hydrochloride" and because evidence of glycosuria was observed in the evening specimens of urine, a second daily injection of regular insulin was decided on. A brand of insulin was chosen which produced the most pronounced intradermal reaction.[34] Ten units was given at noon. With this dose, a mild local reaction was noted at the site of the injection for the next three days. However, this decreased in severity, and eventually no reaction followed the injection of either insulin.

After two weeks of therapy, no localized or generalized reactions to either regular insulin or protamine zinc insulin were noted. Results of determinations of the blood sugar content and of urinalysis attested to the controlled diabetic state. The cutaneous tests were repeated, the same products being used as in the previous tests. The immediate reaction was more intense; the wheals and flares were larger, and pseudopods were present. The wheals subsided rapidly, the swelling, erythema and pruritus remaining for twenty-four hours.

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32. Iletin (Eli Lilly and Company), iletin (Eli Lilly and Company) made from zinc insulin crystals; protamine, zinc and iletin (Eli Lilly and Company); insulin (E. R. Squibb & Sons); protamine zinc insulin (E. R. Squibb and Sons); insulin (Sharp and Dohme, Inc.); protamine zinc insulin (Sharp and Dohme, Inc.); globin insulin with zinc (Burroughs Wellcome & Co.).

33. Sharpe & Dohme, Inc.

34. Insulin (Sharpe & Dohme, Inc.).

At the end of three weeks, during which time the patient was entirely asymptomatic and the diabetes was well controlled by the morning injection of protamine zinc insulin and the noon injection of regular insulin, the use of "pyribenzamine hydrochloride" was discontinued. That same evening the patient complained of a generalized pruritus. The following day swelling, induration, tenderness and pain appeared at the site of the injections of insulin and increased in severity. Small urticarial wheals soon appeared on the extremities. These coalesced into larger hives, and pruritus became severe. Similar larger lesions appeared on the abdomen. Urinalysis at this time showed a persistent orange-red reduction of Benedict's solution in four specimens.

On the following day the patient was once more given the 300 mg. daily dose of "pyribenzamine hydrochloride." Except for mild pruritus and induration at the site of the inoculation with insulin, she became asymptomatic again. Urinalysis now revealed blue and green reduction of Benedict's test solution. Within two days even the local reaction disappeared. At this point the following question arose: Was the histamine antagonist also preventing desensitization while preventing the allergic manifestations to insulin? With this in mind, it was decided to reduce progressively the dosage of the drug. By so doing it was hoped that the severe allergic manifestations would be prevented while a sufficient amount of the insulin would be free to cause a state of "desensitization."

Over a period of four weeks the amount of "pyribenzamine hydrochloride" given was gradually reduced until none was being used. The dosage was determined by the degree of the local reaction to the insulin. With each reduction there were noted local erythema, induration, swelling, pruritus and glycosuria. Maintenance of the reduced dosage soon resulted in the disappearance of the local reaction as well as of the glycosuria.

For the next month A.B. remained symptom free. No "pyribenzamine hydrochloride" was required. The diabetic state was well controlled by diet and by the daily injection of the two doses of insulin.

After this there was an occasional complaint of local pain, swelling and pruritus at the site of the inoculation of the protamine zinc insulin. Lesions which were about 2 cm. in diameter, mildly erythematous and moderately indurated were seen. The symptoms were at their maximum in six hours and entirely gone in twelve to twenty-four hours. "Pyribenzamine hydrochloride" in a single daily dose of 25 to 50 mg. was found to control the occasional local reaction.

The passive transfer test of the skin was repeated. A negative reaction was obtained, indicating either the absence of the skin-sensitizing antibodies in the patient's serum or their presence in but small amounts.

With her adherence to the prescribed diet, the patient's insulin was progressively reduced. The noon dose of regular insulin was discontinued, and the morning dose of protamine zinc insulin was reduced to 15 units. The diabetic state remained well controlled and the patient's general condition good.

## COMMENT

Insulin allergy is reportedly on the increase. Allan and Scherer [3] stated the belief that this was due to sensitization to insulin given in previous years. The importance of the problem for the individual physician called on to treat the diabetic person who is allergic to insulin cannot be minimized.

With the availability of the histamine antagonists, a new method of therapy presents itself. Further clinical trial will be necessary, but that these new drugs have a prominent place in this problem is now apparent.

That "pyribenzamine hydrochloride" was able to control the allergic manifestations of insulin is well demonstrated in this case report. The recurrence of symptoms on withdrawal of the drug is further support of this.

The striking local reaction to the second series of cutaneous tests at a time when the patient was generally asymptomatic as a result of the use of "pyribenzamine hydrochloride" is in agreement with the findings of others. Thus Friedlaender and Feinberg [35] report that the ingestion of "benadryl hydrochloride" did not have any decisive effect on the whealing produced in scratch tests with serial dilutions of histamine or with ragweed extract in sensitive patients. However, when the histamine antagonist was mixed with the antigen or applied to scratches prior to the application of the urticariogenic agent, there was an inhibition of the whealing phenomenon. It would appear that after the oral ingestion of the histamine antagonist there could never be present a sufficient concentration to compete successfully for the receptor cells with the locally liberated histamine.

The development of a persistent glycosuria accompanying the allergic manifestations after withdrawal of the histamine antagonists raises the problem of the relation of insulin refractoriness to allergy. The cases of Glassberg, Foerster and Karr are cited previously. Rudy [36] reports on a patient with mild diabetes in whom an idiopathic urticaria developed and who then required 515 units of insulin in the next twenty-four hours. With the disappearance of the cutaneous lesions, the amount of insulin required was eventually reduced to 10 units on the eleventh day.

Root,[37] working with depancreatized dogs, calculated that 200 to 300 units of insulin would be required by a man of average weight. In cases in which larger amounts are required the disease is considered refractory. Some of the mechanisms producing this state are:

1. Lack of absorption due to induration of the tissues, sclerosis of the vessels or defective circulation.

35. Friedlaender, S., and Feinberg, S. M.: Histamine Antagonists: Effect of Oral and Local Use of β-Dimethylaminoethyl Benzhydryl Ether Hydrochloride on Whealing Due to Histamine, Antigen-Antibody Reactions, and Other Whealing Mechanisms, Therapeutic Results in Allergic Manifestations, J. Allergy **17**:129-141, 1946.

36. Rudy, A.: Urticaria and Insulin Resistance with Reference to Relation of Skin to Carbohydrate Metabolism: Report of Case and Review of Literature, New England J. Med. **204**:791-796, 1931.

37. Root, H. F.: Insulin Resistance and Bronze Diabetes, New England J. Med. **201**:201-206, 1929.

2. Absence of some other essential factor in the process of glycogenesis, i. e., the co-enzyme of Glassberg,[13] the phosphates described by Markowitz [38] and the activating kinase of Himsworth.[39]

3. Loss of tissue in which glycogen can be stored, i. e., involvement of the liver in hemochromatosis, fatty deposition or necrosis.

4. Inhibition of insulin action by infection, pus and toxins. Fever causes an increased requirement.

5. The action of the endocrine antagonists of the pancreas, i. e., the pituitary, thyroid and adrenal glands.

6. Blockage of the diffusion of sugar into the skin. Folin,[40] working with animals, showed that after the intravenous injection of dextrose the skin played an important part in the distribution of sugar in the body. The skin was found to act as a reservoir for the increased amount of sugar. Root[37] concluded from Folin's observations that insulin refractoriness in diabetic patients with disorders of the skin may be caused by a blockage in the diffusion of the sugar into the diseased skin. An increased amount of insulin is required to reduce the elevated blood sugar content.

7. Neutralization of insulin. Lowell [41] presents evidence indicating the presence of two antibodies for crystalline insulin in a patient who was both allergic and resistant to crystalline insulin. A heat-labile allergic antibody which was capable of passively transferring skin sensitivity and an insulin-neutralizing antibody which was heat stabile and capable of destroying the physiologic effect of crystalline insulin were demonstrated. Human and crystalline insulins caused allergic manifestations of the skin, but refractoriness was present to crystalline insulin alone. This evidence, then, plus the knowledge that as well as resistance to insulin in the absence of allergy there can be allergy to insulin in the absence of resistance have led Lowell to conclude that insulin may stimulate the formation of two antibodies, one capable of neutralizing insulin.

38. Markowitz, J.: Relationship of Phosphate and Carbohydrate Metabolism: Effect of Glucose on Excretion of Phosphate in Depancreatised Dogs, Am. J. Physiol. **76**:525-531, 1926.

39. Himsworth, H. P.: Activation of Insulin, Lancet **2**:935-936, 1932.

40. Folin, O.; Trimble, H. C., and Newman, L. H.: Distribution and Recovery of Glucose Injected into Animals, J. Biol. Chem. **75**:263-281, 1927.

41. Lowell, F. C.: Immunologic Studies in Insulin Resistance: Report of Case Exhibiting Variations in Resistance and Allergy to Insulin, J. Clin. Investigation **23**:225-231, 1944; Immunologic Studies in Insulin Resistance: Presence of Neutralizing Factor in Blood Exhibiting Some Characteristics of an Antibody, ibid. **23**:233-240, 1944; Evidence for Existence of Two Antibodies for Crystalline Insulin, Proc. Soc. Exper. Biol. & Med. **50**:167-172, 1942.

A. B., described in this paper, demonstrated the complete inhibition of allergic manifestations with the histamine antagonists. On withdrawal of the latter, not only did the evidences of allergy reappear but so did glycosuria. Because the diabetes was mild, nothing further was noted.

Recommencing the use of the antihistamine drugs resulted in a rapid disappearance of the glycosuria. During the process of desensitization, with reduction of the amount of "pyribenzamine hydrochloride" used, increasing amounts of urinary sugar paralleled the local reaction.

This evidence suggests that the antihistamine agents are of value in some cases of insulin refractoriness associated with insulin allergy. The mechanism of production of the refractoriness may be the local allergic reaction. This tissue response preventing the absorption of the insulin results in an uncontrolled diabetic state. The importance of the antihistaminic agents in preventing these local reactions and thus allowing the free absorption of insulin is readily apparent.

In the case cited in this paper the condition remained well controlled and the patient asymptomatic while the histamine antagonists were being used to control the allergic manifestations of the insulin. At the end of three weeks it was felt that spontaneous desensitization would not occur. Feinberg [42] stated: "Although the preliminary experimental observations of others would indicate that the antagonists of histamine do not interfere with the antigen-antibody reaction or with desensitization, this question has not been conclusively settled." This, then, was the reason for progressively reducing the dosage of "pyribenzamine hydrochloride" to the level at which mild local symptoms were present. Small amounts of the antigen, it was presumed, would remain free to stimulate an antibody response.

That such a program is a successful method of treating insulin allergy is apparent. Whether one obtains complete "desensitization" or merely a state of "hyposensitization," the care of the patient becomes relatively simple. Small doses of the antihistamine drugs will easily control the occasional mild allergic manifestations.

A. B. showed occasional local reactions only at the site of the inoculation of the protamine zinc insulin. Taylor [43] and Wells [44] were unable to demonstrate any antigenic properties of the protamines. Yet the percentage of positive local reactions to protamine zinc insulin is greater

42. Feinberg, S. M.: Histamine and Antihistaminic Agents: Their Experimental and Therapeutic Status, J. A. M. A. **132**:702-713 (Nov. 23) 1946.

43. Taylor: Chemical Studies in Cytolysis, J. Biol. Chem. **5**:311-314, 1908-1909.

44. Wells, H. G.: The Chemical Aspects of Immunity, ed. 2, New York, The Chemical Catalog Company, 1929.

than that to any of the other types of insulin. Kern and Langner [45] expressed the opinion that the addition of protamine to insulin increases the allergy to the latter. Evidence is presented that the addition to a true antigen of a substance in itself possessing no antigenic properties makes sensitization to that antigen easier.

SUMMARY

1. The incidence of true insulin allergy is small. A generalized reaction develops in approximately one person in a thousand using insulin.

2. Insulin is a protein substance capable of antigenic activity.

3. The importance of insulin allergy is demonstrated by case reports from the literature.

4. Mention is made of the methods used in attempting to control insulin allergy.

5. Brief mention is made of the development of the histamine antagonists.

6. A case of insulin allergy is reported wherein the allergic manifestations were controlled with the newer histamine antagonists. A method for "hyposensitization" and, possibly, desensitization is described.

7. Insulin refractoriness associated with insulin allergy may be the result of impaired absorption from the site of injection due to local tissue reaction. Further investigation is awaited.

Department of Metabolism, Michael Reese Hospital.

45. Kern, R. A., and Langner, P. H., Jr.: Protamine and Allergy: Nature of Local Reactions After Injections of Protamine Zinc Insulin; Induction of Sensitivity to Insulin by Injections of Protamine Zinc Insulin, J. A. M. A. **113**: 198-200 (July 15) 1939.

# HETEROPHILE ANTIBODY TITER IN DISEASES OTHER THAN INFECTIOUS MONONUCLEOSIS

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TO DATE, the heterophile antibody or Paul-Bunnell test has been considered one of the few specific laboratory tests, most investigators stating that only infectious mononucleosis, serum sickness or injections of liver can cause a diagnostic agglutination titer of 1:32 or higher by the Paul-Bunnell method or of 1:56 or higher by the more commonly used Davidsohn modified technic.[1]

In the laboratory of Research Hospital, my colleagues and I have in the past twenty-three months made a total of five hundred and three tests on 220 different patients, using exclusively the Davidsohn technic, with readings taken after overnight incubation in the refrigerator. Since many of these tests have been done on outpatients whose complete records were not accessible, the study is limited to 141 patients, representing only those for whom diagnosis was made after examination of tissue either on their admission to Research Hospital or on their examination at the Research Clinic. In this group of 141 patients are included 31 with clincally and/or hematologically proved infectious mononucleosis, 6 with Hodgkin's disease, 13 with leukemia of all types, 1 with polycythemia, 29 with tuberculosis, 8 with sarcoma other than Hodgkin's type and 53 with miscellaneous diseases in which there was no clinical or hematologic evidence of mononucleosis.

The table illustrates the frequency of various titers in the 31 patients with infectious mononucleosis and in the 57 with diseases other than infectious mononucleosis. The high incidence of the so-called diagnostic titers in diseases other than infectious mononucleosis is impressive.

The highest titers, of course, occur in infectious mononucleosis. What we wish to draw attention to, however, are the so-called diagnostic titers which have occurred in patients with other diseases.

## DIAGNOSTIC TITERS IN VARIOUS DISEASES

1. *Hodgkin's Disease.*—Kolmer and Boerner[2] stated: "Positive reactions do not occur in the leukemias, Hodgkin's disease, etc." However, in a total of eighteen tests on 6 patients examined here, we have

1. Kaufman, R. E.: Heterophile Antibody Reaction in Infectious Mononucleosis, Ann. Int. Med. **2**:230-251 (Aug.) 1944.

2. Kolmer, J. A., and Boerner, F.: Approved Laboratory Technic, ed. 4, New York, D. Appleton-Century Co., Inc., 1945, pp. 643-644.

found three agglutinations of 1:224, six agglutinations of 1:112 occurring in 2 different patients, seven agglutinations of 1:56 occurring in 6 different patients and no negative reading for any of the 6 patients. Sixteen of these eighteen tests are in the "diagnostic" range.

In this connection, Kaufman in 1944 [1] reported that in his series of patients examined by the Davidsohn technic a rare titer of 1:112 was found in cases of scarlet fever, Hodgkin's disease and primary anemia, with also a titer of 1:224 in a case of Hodgkin's disease. He considered these results of no significance.

*Heterophile Antibody Titers in Infectious Mononucleosis and Other Diseases*

| Disease | No. of Cases | No. of Readings | Frequency of Titers | | No. of Readings in Diagnostic Range (1/56 or Higher) |
|---|---|---|---|---|---|
| Infectious mononucleosis | 31 | 117 | 1 × 14 | 37 × 448 | 113 of 117 |
| | | | 3 × 28 | 6 × 896 | |
| | | | 6 × 56 | 3 × 1,792 | |
| | | | 16 × 112 | 1 × 3,584 | |
| | | | 43 × 224 | 1 × 1,436 | |
| Hodgkin's disease | 6 | 18 | 2 × 7 | 6 × 112 | 16 of 18 |
| | | | 7 × 56 | 3 × 224 | |
| Agranulocytosis | 3 | 10 | 3 × Neg. | 2 × 28 | 2 of 10 |
| | | | 2 × 7 | 1 × 56 | |
| | | | 1 × 14 | 1 × 112 | |
| Lymphatic leukemia | 2 | 8 | 1 × 7 | | 0 of 8 |
| | | | 5 × 14 | | |
| | | | 2 × 28 | | |
| Monocytic leukemia | 2 | 8 | 1 × 14 | 4 × 112 | 6 of 8 |
| | | | 1 × 28 | 1 × 448 | |
| | | | 1 × 56 | | |
| Myelogenous leukemia | 6 | 45 | 9 × 7 | 17 × 56 | 24 of 45 |
| | | | 6 × 14 | 6 × 112 | |
| | | | 6 × 28 | 1 × 224 | |
| Polycythemia | 1 | 3 | 1 × 28 | | 2 of 3 |
| | | | 1 × 56 | | |
| | | | 1 × 112 | | |
| Sarcoma other than Hodgkin's Disease | 8 | 23 | 11 × Neg. | 3 × 112 | 9 of 23 |
| | | | 3 × 14 | 1 × 224 | |
| | | | 4 × 56 | 1 × 448 | |
| Tuberculosis | 29 | 45 | 1 × 14 | 10 × 112 | 27 of 45 |
| | | | 17 × 28 | 7 × 224 | |
| | | | 9 × 56 | 1 × 448 | |

2. *Agranulocytosis.*—In a total of ten tests on 3 patients we found one agglutination at 1:112 and one at 1:56; there were three negative reactions, all of which occurred in a patient who in her fourth test had an agglutination of 1:7. In another case the sequence was 56, 112, 28, 14 and 7. Two of these ten titers are "diagnostic."

3. *Lymphatic Leukemia.*—In a total of eight readings on 2 patients we found no negative reactions but no agglutination over 1:28.

In this connection, Kent [3] reported in 1940 a case of fatal chronic myelogenous or chronic monocytic leukemia in a 14 year old boy with a 1:4096 titer by the original Paul-Bunnell technic (1:32 diagnostic).

3. Kent, C. F.: "False" Positive Paul-Bunnell (Heterophile) Reaction? Am. J. Clin. Path. **10**:576-580 (Aug.) 1940.

He raised a question at that time in the title of his report: "'False' Positive Paul-Bunnell (Heterophile) Reaction?"

Furthermore, Bethell, Sturgis, Rundles and Meyers,[4] in a 1946 review of the literature on infectious mononucleosis, cited the report by Etcheverry of a titer of 1:896 in a case of lymphatic leukemia; the author attributed the titer to injections of liver which the patient had received.

4. *Monocytic Leukemia.*—In a total of eight readings on 2 patients with monocytic leukemia 1 of the patients had titers of 448, 112, 112, 112 in the four weeks prior to death and the other titers of 14, 28, 56, and 112, representing a progressive weekly rise till the time of death. Of these eight readings, six fall within the diagnostic range.

5. *Myelogenous Leukemia.*—Of a total of forty-five readings in 6 of our patients, twenty-four are in the diagnostic range. No correlation could be noted between the titers and any change in the differential counts of these patients.

As a matter of fact, in this group of cases is one of the early ones which stimulated interest in the "false" heterophile reaction. This is the case of a 42 year old man with a history of fever and chills for two days prior to his first admission to the hospital on April 10, 1946. A roentgenogram of the chest showed a possible atypical pneumonia. He was treated with sulfadiazine and penicillin and dismissed on April 13. When readmitted on July 6, he was complaining of pain in the chest, present ever since his previous discharge. His temperature was 100 to 101.8 F. Several examiners found no abnormal physical signs. The roentgenologic appearance of the chest was essentially the same as in April. The heterophile titer at which agglutination was positive on July 8 was 1:112; the blood count showed a hemoglobin content of 89 per cent; a red blood cell count of 4,400,000, and a white blood cell count of 12,700, with 27 segmented neutrophils, 12 stab forms, 11 eosinophils and 50 lymphocytes. Four days later, the heterophile agglutination was 1:224, with a white blood cell count of 16,250 now showing 17 segmented neutrophils, 17 stab forms, 1 juvenile form, 11 myelocytes, 4 premyelocytes, 6 eosinophils, 35 lymphocytes, 2 monocytes, 6 blastocytes, 1 unidentified cell and several smudges.

Several clinicians who saw the patient at this time persisted in the diagnosis of infectious mononucleosis because of the titers of 112 and 224; however, this titer then regressed to 56 on four readings, 28 on three readings and 14 on 1 reading, while the myelogenous series of cells gradually became more immature until he died on Sept. 16, 1946, of full-blown acute myelogenous leukemia.

4. Bethell, F. H.; Sturgis, C. C.; Rundles, R. W., and Meyers, M. C.: Blood: A Review of the Recent Literature; Infectious Mononucleosis, Arch. Int. Med. **77**:80-91 (Jan.) 1946.

6. *Polycythemia.*—Two of our three readings taken in 1 case of polycythemia fall within the diagnostic range. Since there is only 1 case in this group, we can give this little if any statistical importance.

7. *Sarcoma Other Than Hodgkin's Disease.*—Nine of twenty-three readings on the 8 patients with sarcoma other than Hodgkin's type are in the diagnostic range. Interestingly, in 1 of 2 cases of reticulum cell sarcoma there were nine repeated negative readings, with never a positive reaction, while in the other the readings were 448, 224, 112 and negative. In 1 case of fibrosarcoma of the abdominal wall the titer was 1:112 on one occasion and 1:56 on two occasions, and in a case of follicular lymphoblastoma there was a reading of 1:112. The 1 patient with myxosarcoma in the group had two readings of 1:56 occurring simultaneously with a myelogenous leukemoid reaction in the peripheral blood smear. In the 3 cases of lymphosarcoma there were three readings at 1:14, one at 1:56, and one negative reaction.

8. *Tuberculosis.*—Since twenty-seven of our forty-five readings on 29 tuberculous patients are in the "diagnostic" range, we consider this an important statistical group. Two young men with fever and chills were found to have a titer of 1:224 with no other evidence of infectious mononucleosis. Both subsequently died after a brief stormy course of miliary tuberculosis. Since few patients with tuberculosis are admitted to Research Hospital, we obtained permission to select patients at the Leeds Tuberculosis Sanatorium for further study.

We selected 12 patients in the terminal stages of tuberculosis and another 12 who were ready to be dismissed with their disease completely arrested. In the terminal group we found 4 patients with a titer of 1:224, 4 with a titer of 1:112 and 4 with a titer of 1:28. In the arrested group, we found essentially the same, i. e., 2 patients with a titer of 1:224, 4 with a titer of 1:112, 3 with a titer of 1:56 and 3 with a titer of 1:28. Thus in all cases of tuberculosis, both active and arrested, which we have investigated there has been a positive titer, and in twenty-seven of forty-five tests on these 29 patients we have found a "diagnostic" level.

Bernstein [5] in 1940 wrote: "One of Longcope's cases developed tuberculous pleurisy six years later; a physician, not included in our group, died three year later of tuberculous meningitis. There is no reason to assume that these represent anything more than coincidences that might occur in any group of young people." Later in the same report, he says: "An occasional increased titer has been reported in scarlet fever, rubeola, tuberculosis and filariasis, but such events are excessively uncommon."

9. *Miscellaneous Diseases, With no Evidence of Infectious Mononucleosis.*—Throughout this study, patients with fever of any type or

5. Bernstein, A.: Infectious Mononucleosis, Medicine **19**:85-159 (Feb.) 1940.

with a blood smear varying from the normal were candidates for the test. Some of our more interesting findings in this group were as follows: A titer of 1:224 was found in 1 case of allergy, 1 case of staphylococcemia from a carbuncle, a case of a 59 year old woman with a history of pleurisy and a diagnosis of tuberculosis in 1936 but with no evidence on roentgenologic examination at this time and a case of a 46 year old woman with evidence of old healed tuberculosis in a roentgenogram and with a monocyte count of 50 per cent. A titer of 1:112 was found in 1 case of toe infection due to Staphylcoccus albus in a diabetic patient, thyrotoxicosis, splenic thrombocytopenia, chronic nephritis, aplastic anemia, diverticulitis of the colon, and migraine headache, in 1 patient receiving injections of liver and in 1 patient with quiescent rheumatic fever.

Agglutination in lower dilutions was obtained in a wide variety of cases.

## COMMENT

From the data reviewed, we gain the impression that the heterophile antibody or Paul-Bunnell test is not as specific as it is generally considered to be. This statement is all the more interesting when the comment made by Paul and Bunnell themselves in their early report of 1932 [6] is reviewed:

> . . . in spite of the fact that the limits of the reaction which we have described have not been tested, it would seem to be of diagnostic value. In a sense, however, it appears to be of more theoretical than practical interest. Theoretical interest centers about the fact that heterophile antibodies may be produced or enhanced during the course of human infectious diseases, and in one disease in particular, in which the etiology has not been established. Furthermore, that 2 clinical entities with widely differing symptomatology, such as serum sickness and infectious mononucleosis, would elicit the same type of serologic response is also worthy of interest. . . . On the other hand, it is also conceivable that the phenomenon which we have described is in the nature of an isoagglutinin response to the presence of an excess of abnormal cells either present in the blood or elsewhere.

Our data would tend to bear out this last supposition, for all the diseases in our series which gave the so-called diagnostic titers—Hodgkin's disease and other sarcomas, blood dyscrasias and tuberculosis—are diseases characterized by abnormal cells present either in the blood or elsewhere.

## SUMMARY AND CONCLUSIONS

1. Heterophile antibody titers were determined by the Davidsohn technic in a total of 57 patients suffering from Hodgkin's disease and other sarcomas, blood dyscrasias or tuberculosis.

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6. Paul, J. R., and Bunnell, W. W.: The Presence of Heterophile Antibodies in Infectious Mononucleosis, Am. J. M. Sc. **183**:90-104 (Jan.) 1932.

2. So-called diagnostic titers were found in a significant number of patients suffering from Hodgkin's disease, monocytic or myelogenous leukemia, several sarcomas and tuberculosis.

3. Patients showing a heterophile antibody titer of 1 : 56 or over and with no present or past clinical evidence of infectious mononucleosis or serum sickness deserve further study to determine the presence of organic disease. These diagnostic titers should not be dismissed as "incidental," but rather they should indicate, much in the manner of the increased sedimentation rate, further probing for a disease in which there are "abnormal cells present in the blood or elsewhere."

# MIXED INFECTION IN SUBACUTE BACTERIAL ENDOCARDITIS

## Report of Two Cases

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SUBACUTE bacterial endocarditis caused by more than one micro-organism is uncommon. In 1942, Orgain and Poston [1] described 6 cases of mixed infection; since their report several additional cases [2] have been reported. The recognition of mixed infections is of more than theoretic interest in view of the present choice of antibiotics. Prompt treatment with the appropriate drug, in adequate dosage, can be facilitated when all the micro-organismss concerned in the infection are identified bacteriologically and when their sensitivities to the antibiotics are determined. These considerations apply to the 2 cases of mixed infection in subacute bacterial endocarditis recently encountered in Mount Sinai Hospital.

### REPORT OF CASES

CASE 1.—S. G., a 26 year old man, sought admission to the hospital for the first time on Sept. 7, 1946, because he had had a "blind spot" in the left eye for one week. At the age of 7 years the patient had had attacks of chorea, which recurred yearly until the age of 12. A residual cardiac murmur had been noted. For the past five years, the patient had had a slight elevation in blood pressure.

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From the Division of Bacteriology Laboratories and First Medical Service of Dr. George Baehr, The Mount Sinai Hospital, New York.

1. Orgain, E. S., and Poston, M. A.: Mixed Infections in Bacterial Endocarditis, Am. Heart J. **23**:823-836 (Dec.) 1942.

2. (*a*) Moore, R. A.: The Cellular Mechanism of Recovery After Treatment with Penicillin, J. Lab. & Clin. Med. **31**:1279-1293 (Dec.) 1946. (*b*) Favour, C. B.; Janeway, J. G.; Gibson, J. G., II, and Levine, S. A.: Progress in Treatment of Subacute Bacterial Endocarditis, New England J. Med. **234**:71-77 (Jan. 17) 1946. (*c*) Galbreath, W. R., and Hull, E.: Sulfonamide Therapy of Bacterial Endocarditis: Results in Forty-Two Cases, Ann. Int. Med. **18**:201-203 (Feb.) 1943. (*d*) Jones, S. H., and Tichy, F.: Bacterial Endocarditis Treated with Penicillin: Observations in Nine Cases, New England J. Med. **236**:729-736 (May 15) 1947. (*e*) Geiger, A. J.: Penicillin Therapy in Subacute Bacterial Endocarditis, Mississippi Valley M. J. **69**:2-16 (Jan.) 1947. (*f*) MacLean, H., and Howell, K. M.: Two Coexistant Strains of Viridans Streptococci Isolated from Blood Cultures by Penicillin Sensitivity Tests, Am. J. M. Sc. **214**:53-55, 1947. (*g*) Paul, O.; Bland, E. F., and White, P. D.: Bacterial Endocarditis, New England J. Med. **237**:349-354, 1947.

occasional periods of arrhythmia and tachycardia; the latter responded to treatment with digitalis.

Fever, chills, anorexia and cough began two weeks prior to admission. One week later, the patient noted impaired vision in the left eye. A tender node appeared in the left forefinger. Three hundred thousand Oxford units of penicillin in wax and oil were administered twenty-four hours prior to admission.

*Examination.*—On admission the patient was observed to be in good nutritional condition. His temperature was 101 F., pulse rate 120 and blood pressure 130 systolic and 70 diastolic. Vision was absent in the lower nasal field of the left eye. The fundus showed narrowing of the supertemporal artery, and there was slight retinal edema in the upper temporal quadrant of the affected eye. The heart was enlarged to the left. A coarse systolic murmur and thrill at the apex transmitted to the axilla, and an apical presystolic murmur and a diastolic murmur at Erb's

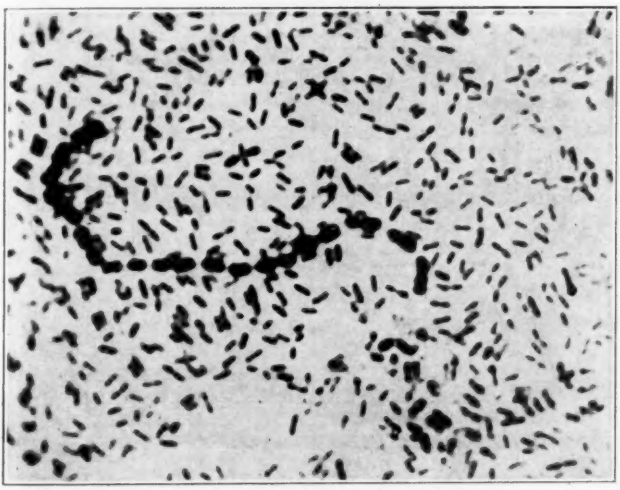

Fig. 1 (case 1).—Str. viridans and C. pseudodiphthericum (hoffmannii). Gram stain of a twenty-four hour subculture on blood agar plate from the original blood culture (× 2,800).

point were observed. The abdomen was normal. There was an Osler node at the tip of the left forefinger. The peripheral pulse had the bounding quality of a water hammer. Fluoroscopy confirmed the ventricular enlargement on the left side, prominent pulmonary artery segment, auricular enlargement on the left side and some cardiac enlargement on the right side. The electrocardiogram revealed regular sinus rhythm, wide and notched P waves and S-T elevation in all leads. The hemoglobin was 90 per cent (Sahli), red blood cell count 4,950,000 and white blood cell count 6,800, with 66 per cent segmented and 3 per cent nonsegmented polymorphonuclear leukocytes, 23 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils. The erythrocyte sedimentation rate was 44 mm. per hour (Westergren). The urine contained no albumin and no red blood cells. The level of urea nitrogen in the blood was 10 mg. and sugar 80 mg. per hundred cubic centimeters. The Wassermann reaction was negative, Streptococcus viridans

(alpha) was cultivated from the throat. Roentgenologic examination of the chest confirmed the fluoroscopic observations. Roentgenologic examination of the sinuses revealed evidence of chronic inflammation.

*Course.*—The patient continued to have a temperature between 101 and 102 F. for the following two weeks. The white blood cell count rose to 13,000, and evidence of a splenic infarct appeared, although the spleen itself was never palpable. The clinical diagnosis was subacute bacterial endocarditis. Repeated blood cultures were made in an effort to discover the responsible micro-organism before treatment was instituted.

*Bacteriologic Observations.*—The routine technic for blood cultures employed in the department of bacteriology of this hospital is as follows: Under strict aseptic conditions, 23 cc. of the patient's blood is drawn from an anterior cubital

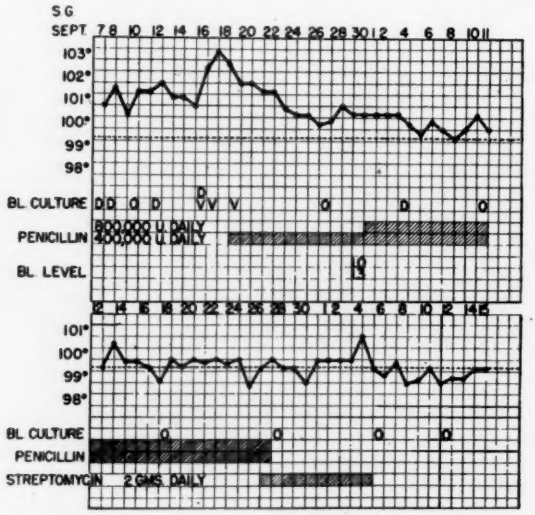


Fig. 2.—Summary of data in case 1.

vein; 15 cc. is divided equally among three 100 cc. Erlenmeyer flasks, the first containing yeast veal infusion broth at $p_H$ 7.4, the second, 2 per cent dextrose veal infusion broth at $p_H$ 7.4 and the third, plain veal infusion broth with para-aminobenzoic acid at $p_H$ 7.4. Two cubic centimeters of blood is mixed with each of two tubes containing 12 cc. of 2 per cent dextrose veal infusion agar at $p_H$ 7.4. Two cubic centimeters is mixed with a tube containing 12 cc. of plain veal infusion agar at $p_H$ 7.4, and 2 cc. is put into a tube containing 10 cc. of cooked liver broth at $p_H$ 7.4, which is sealed with 2 cc. of sterile petrolatum. The three flasks are kept in an atmosphere of air containing approximately 3.5 per cent of carbon dioxide, which is obtained by placing a lighted candle in a glass jar fitted with a petrolatum sealed cover.

Figure 2 demonstrates the significant observations in the blood cultures prior to and following treatment. Both diphtheroids and Str. viridans were obtained. The diphtheroids were short gram-positive bacilli in characteristic diphtheroid arrangement. The colonies were nonhemolytic, aerobic and facultatively anaerobic.

Glucose, sucrose, maltose, lactose and mannite were not fermented. There was no change in litmus milk, nor was gelatin liquefied. The streptococcus showed alpha hemolysis on the blood plate, was insoluble in bile, did not grow in 20 per cent bile broth or on Endo mediums and was killed by heating at 60 C. for twenty minutes.

At first the diphtheroids were considered to be contaminants, since they were not consistently cultured in all mediums. Str. viridans was finally isolated in the fifth, sixth and seventh blood cultures. The sensitivity of that organism to penicillin was as high as that of the standard strain, Staphylococcus aureus H, 0.02 units of penicillin per cubic centimeter being required for complete inhibition. Treatment was started with 400,000 Oxford units of penicillin daily, i. e., 50,000 Oxford units administered intramuscularly every three hours, on September 21. By the ninth day of treatment it was evident that the patient was not responding as well as might be expected from the high sensitivity of the organism. The dosage was therefore doubled to 800,000 Oxford units daily. The levels of penicillin in the blood fifteen minutes after administration of 100,000 Oxford units intramuscularly on two occasions were 1.0 and 1.3 units per cubic centimeter. Three hours after the injection was given, levels of 0.05 and 0.13 units per cubic centimeter were still present. With the increased dosage, the patient's temperature dropped to normal by the thirteenth day. On the same day, a diphtheroid was isolated once again. This organism was susceptible to 0.1 unit of penicillin per cubic centimeter, i. e., five times the resistance of the standard organism, and to 0.6 unit of streptomycin per cubic centimeter, i. e., three times the resistance of the standard organism, Staph. aureus (Smith). The diphtheroid was 50 per cent inhibited by 70 mg. per hundred cubic centimeters of sulfadiazine and not completely inhibited by 100 mg. per hundred cubic centimeters. It was identified as Corynebacterium pseudodiphthericum (hoffmannii). Since this was the fifth isolation of the diphtheroid, it was thought that this organism might be an additional infectious agent. The presence of diphtheroids also could explain the delayed response, in view of the fact that its resistance to penicillin was greater than that of Str. viridans. Treatment was continued for a total of six weeks. Twelve grams of streptomycin was given for six days, because of the susceptibility of the diphtheroids to streptomycin. Five subsequent blood cultures werer negative. The patient was discharged on November 16. Additional blood cultures, made during return visits to the outpatient department, were sterile. The patient has been well for one year from the time of discharge.

*Comment.*—The pleomorphism of both organisms is well known.[3] It was necessary to eliminate the possibility that the diphtheroid and streptococcus forms were morphologic variants of one micro-organism. C. pseudodiphthericum and Str. viridans were therefore subcultured in broth and on solid mediums repeatedly for six weeks; the two organisms retained their morphologic and cultural characteristics. Review of the chart shows that the corynebacterium was isolated from five different blood cultures and Str. viridans from three different cultures. Furthermore, on one occasion both organisms were seen in the same

3. Libman, E., and Friedberg, C. K.: Subacute Bacterial Endocarditis, in Christian, H. A.: Oxford Loose-Leaf Medicine, New York, Oxford University Press, Inc., 1941. Jensen, L. B., and Morton, H. B.: The Diphtheroid Phase of Streptococci, J. Infect. Dis. **49**:425 (Nov.) 1931.

culture. Thus, the evidence points toward mixed infection. The clinical course of the patient demonstrated that a dosage of penicillin ordinarily sufficient to inhibit the organism of lower resistance was inadequate to inhibit the organism of higher resistance in vivo.

CASE 2.—D. N., a woman aged 39, had had rheumatic fever at the age of 12 years. One month before the present admission, an infection of the upper part of the respiratory tract developed. Chills and fever, accompanied with loss of weight, cough and swelling and tenderness of the right middle finger, persisted until her admission on Nov. 2, 1946, despite six days of treatment with small doses of penicillin. A blood culture made one week prior to admission was negative.

*Examination.*—The temperature was 104 F., pulse rate 100, blood pressure 110 systolic and 55 diastolic and respiratory rate 20. Petechiae were seen in the left conjunctival sac and in the left fundus. A few moist rales were heard over the base of the left lung. The heart appeared enlarged to percussion, and murmurs of mitral and aortic insufficiency were present. The fingers were clubbed, and the left index finger was tender. There were petechiae on the right side of the chest, below the breast. Kyphoscoliosis of the dorsal and lumbar aspects of the spine, with convexity to the right side, was present.

*Laboratory Observations.*—The hemoglobin was 72 per cent, red blood cell count 3,900,000 and white blood cell count 23,900, with 72 per cent adult polymorphonuclear leukocytes, 14 per cent nonsegmented polymorphonuclear cells, 11 per cent lymphocytes and 3 per cent monocytes. The urine contained a trace of albumin and occasional white and red blood cells. The erythrocyte sedimentation rate was 48 mm. per hour (Westergren). The level of urea nitrogen in the blood was 11 mg. per hundred cubic centimeters. Venous pressure of the antecubital vein was 85 mm., and saccharine circulation time was 13 seconds. An electrocardiogram showed: regular sinus rhythm, left axis deviation, a small Q wave in leads I and II and a QRS interval of 0.11 to 0.12 seconds.

Figure 3 demonstrates the results of blood cultures, which revealed the presence of two different organisms. Hemophilus parainfluenzae was obtained on the first and third hospital days and Str. viridans on the second day. The first microorganism was a tiny gram-negative pleomorphic bacillus, which grew slowly aerobically, anaerobically and in 3.5 per cent carbon dioxide. In liquid mediums the organism assumed a rough granular appearance. It was nonhemolytic and grew on blood and chocolate agar, but required the V factor for survival on plain mediums. Nitrates were reduced, and glucose was fermented. Agglutination with Fothergill's polyvalent influenza antiserum was positive in a dilution of 1 to 128. The precipitin reaction with the same antiserum was positive in a dilution of 1 to 16. A precipitin test of the organism against the patient's serum elicited a positive reaction in a dilution of 1 to 32. Agglutinations of Brucella abortus and Brucella melitensis, H. influenzae alpha and beta and two parainfluenzae strains with the patient's serum were all negative. The H. parainfluenzae was susceptible to 2.5 Oxford units of penicillin per cubic centimeter, or one hundred and twenty-five times as resistant as the standard strain, and to 0.8 unit of streptomycin per cubic centimeter, or four times the resistance of the standard strain. The gram-positive coccus in chains had all the characteristics of Str. viridans. It was susceptible to 0.2 unit of penicillin per cubic centimeter, or ten times the resistance of the standard strain, and to 8.0 unit of streptomycin per cubic centimeter, or forty times the resistance of the standard strain. Both organisms were 50 per cent

inhibited by 30 mg. per hundred cubic centimeters of sulfadiazine and not completely inhibited by 100 mg. per hundred cubic centimeters.

*Course.*—The patient was acutely sick on admission; her temperature ranged between 104 and 106 F. for the first two days. Treatment with penicillin was begun on the morning of the third hospital day, before studies of sensitivity had been made, the dosage being 300,000 Oxford units given intramuscularly every three hours. Levels of penicillin in the blood of 8.0 and 10 units per cubic centimeter were obtained fifteen minutes following intramuscular injection; 1.3 and 2.0 units per cubic centimeter were still present three hours following administration of the injection. There was an immediate clinical improvement, but not a complete remission. The temperature persisted up to 101 to 102 F., although blood cultures were sterile.

The level of urea nitrogen in the blood remained normal. The kidney was able to concentrate up to a specific gravity of 1.034. The fasting blood sugar was 95

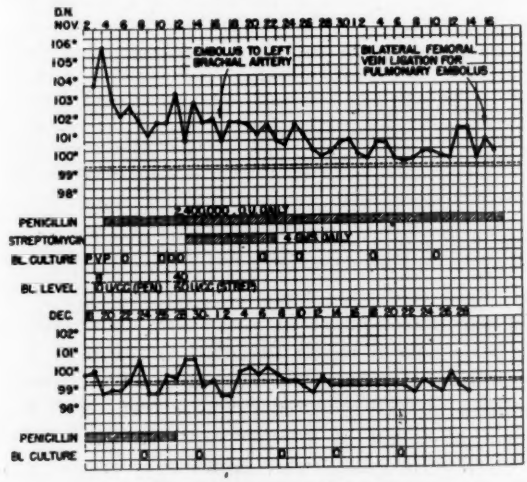


Fig. 3.—Summary of data in case 2.

mg. and the total protein 6.7 Gm. per hunderd cubic centimeters. The Kahn reaction was reported to be 3 plus and 2 plus on three different occasions. No macrophages were observed in blood taken from the ear.

Treatment with streptomycin was instituted on September 13, in view of the sensitivity of H. parainfluenzae to this drug. One gram every six hours was given intramuscularly for ten days. Levels of streptomycin in the blood ranged from 40 to 60 units per cubic centimeter, and the urine contained up to 1,300 units per cubic centimeter. The temperature was not altered during treatment with streptomycin, but this may have been partly the result of thrombophlebitis subsequent to the lodging of an embolus in the left brachial artery on September 16. The drug itself may provoke a pyrogenic reaction, which subsides after cessation of treatment.

Paresthesia and, finally, numbness appeared in the left hand within twelve hours. Pulsation was not palpable, and the extremity became cold. Intravenous treatment with papavarine, stellate ganglion block and subsequent physical therapy

brought slow improvement. Oscillometric readings were 0.25 units. Horner's syndrome developed on the left side as a result of the ganglion block.

Blood cultures remained sterile, although penicillinase was added to inhibit the effects of the high concentration of penicillin. The temperature dropped to lower levels after a ten day course of streptomycin. The patient continued to improve slowly, the temperature remaining about 100 F. during the fifth week of treatment.

On December 15, the patient noted sudden dyspnea, pleuritic pain on the left side, rapid respiration and tachycardia. The temperature rose to 101 F., and signs of consolidation appeared over the base of the left lung. Roentgenologic examination revealed faint infiltrations in the lower lobe of the right lung and Fleischner's lines in the midportion of the left lung and the lower lobe of the right lung. Tenderness was present in both calves. Both femoral veins were ligated. The femoral vein on the left side was observed to be acutely inflamed and thickened. Dicumarol was given, and the prothrombin index remained between 35 and 45 per cent for two weeks. There were several subsequent attacks of tenderness in the left calf, with superficial phlebitis over the left ankle, which subsided spontaneously. Because of the persistent rales at the base of the right lung, it was felt that the patient might be experiencing congestive failure, despite normal venous pressure and circulation time. Digitalis was therefore given. Treatment with penicillin was stopped after eight weeks, yet improvement continued. The patient was discharged one month later, on Jan. 29, 1947, and has subsequently been seen in the follow-up clinic. Blood cultures made up to one year following completion of treatment have remained sterile.

*Comment.*—Hunter and Duane,[4] in reviewing the results of antibiotic therapy in subacute bacterial endocarditis caused by gram-negative organisms, have noted conflicting results. They reported 2 cases in which treatment was successful, 1 in which the disease was caused by H. parainfluenzae and in which sulfadiazine was used and 1 in which the disease was caused by an unusual gram-negative bacillus and in which sulfadiazine and streptomycin were used. Priest and his co-workers[5] described a case of infection with H. parainfluenzae in their series in which good results were achieved by treatment with a combination of penicillin and sulfamerazine, although treatment with each drug alone had failed to sterilize the blood stream. Paul, Bland and White[2g] reported the apparent recovery of a patient with endocarditis due to H. parainfluenzae following seventeen days of treatment with streptomycin.

Our patient was acutely ill on admission. The early use of antibiotics was probably a life-saving measure. Two organisms were obtained in three successive blood cultures, although both were never grown in the same culture. H. parainfluenzae grew in all mediums twice and Str. viridans once. In view of the heavy infection (30

4. Hunter, T. H., and Duane, R. B., Jr.: Subacute Bacterial Endocarditis Due to Gram-Negative Organisms, J. A. M. A. **132**:209-211 (Sept. 28) 1946.

5. Priest, W. S.; Smith, J. M., and McGee, C. J.: Penicillin Therapy of Subacute Bacterial Endocarditis, Arch. Int. Med. **79**:333-359 (March) 1947.

colonies per cubic centimeter) with the latter organism, it was assumed that Str. viridans was probably involved in the valvulitis and was not merely transitory. The sensitivities to antibiotics were of interest. H. parainfluenzae was resistant to penicillin, but was moderately sensitive to streptomycin. On the other hand, Str. viridans was resistant to streptomycin, but was only moderately sensitive to penicillin. Neither was susceptible to sulfadiazine. Large doses of both penicillin and streptomycin were administered, and high concentrations in the blood were obtained. The level of streptomycin in the blood reached forty times the concentration necessary to inhibit the parainfluenzae in vitro. The level of penicillin in the blood reached fifty times the concentration necessary to inhibit the viridans in vitro. Obviously, both antibiotics were essential in this case, and, in view of the studies of sensitivity, high dosages were especially necessary.

## SUMMARY

Two cases of subacute bacterial endocarditis with mixed infection which responded favorably to antibiotic therapy are reported.

In the first case Corynebacterium pseudodiphthericum (hoffmannii) and Streptococcus viridans were present, the former having higher resistance to penicillin than the latter. When the corynebacterium was recognized as one of the infecting agents, penicillin was given in adequate dosage.

In the second case Str. viridans and Hemophilus parainfluenzae were present. The simultaneous use of two antibiotics was necessary. This represents the third reported case of subacute bacterial endocarditis due to a gram-negative bacillus which was successfully treated with streptomycin.

It is suggested that mixed infection in subacute bacterial endocarditis may be more frequent than is reported. Adequate selection of suitable antibiotics may require identification of all the organisms involved in a given infection.

NOTE: Since this report was submitted, two articles appeared on the use of streptomycin in bacterial endocarditis due to gram-negative bacilli:

Hunter, T. H.: Use of Streptomycin in Treatment of Bacterial Infection, Am. J. Med. **2**:436-442 (May) 1947.

Massel, B. F.; Zeller, J. W.; Dow, J. W., and Harting, D.: Streptomycin Treatment of Bacterial Endocarditis: Report of a Case, New England J. Med. **238**:464-466 (April 1) 1948.

Hunter presents 3 cases of endocarditis due to gram-negative bacilli in which the favorable results were attributed at least in part to streptomycin. Massel and others report a case in which the patient recovered after receiving only 13.5 Gm. of streptomycin in six and a half days.

# PRIMARY SYSTEMIC AMYLOIDOSIS SIMULATING CONSTRICTIVE PERICARDITIS

## With Steatorrhea and Hyperesthesia

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AND
WRIGHT ADAMS, M.D.
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AMYLOIDOSIS has been divided into the following types: (1) that which is secondary to chronic suppurative diseases, tuberculosis and occasionally rheumatoid arthritis; (2) a type which sometimes accompanies multiple myeloma; (3) a form in which the amyloid is confined to one organ or tissue, and (4) primary systemic amyloidosis. The last-named type is distinctive in that: (1) it is not associated with suppuration, tuberculosis, rheumatoid arthritis or multiple myeloma; (2) it usually does not involve the liver, kidneys, adrenals or spleen to a marked degree; (3) the amyloid is deposited in the heart, lungs, gastrointestinal tract, mucous membranes, skin and striated muscles; (4) the amyloid is capricious in its staining reactions; (5) it often forms nodular amyloid tumors,[1] and (6) patients afflicted with this disease live longer on an average than those with secondary amyloidosis.

This is the fifty-fourth reported case of primary systemic amyloidosis, a case which presents some unusual features of an unusual disease and which until the postmortem examination appeared to be one of constrictive pericarditis.

### REPORT OF A CASE

*History.*—B. I., a 46 year old shoe clerk, was admitted to Billings Hospital on July 18, 1946, complaining of edema of the legs, distention of the abdomen and hypersensitiveness of the skin. He was first seen at this hospital in 1935, complaining of slight "heaviness" in the chest. On roentgen examination a neurofibroma was found in the right posterior portion of the mediastinum. This was removed without incident at another hospital in 1939.

From 1937 to 1944 the patient was treated by desensitization for fall pollen disease, consisting of hay fever, asthma and giant urticaria, which had been present since 1927.

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From the Department of Medicine, Division of Biological Sciences, University of Chicago.

1. Koletsky, S., and Stecher, R. M.: Primary Systemic Amyloidosis: Involvement of Cardiac Valves, Joints and Bones, with Pathologic Fracture of the Femur, Arch. Path. **27**:267 (Feb.) 1939. Steinhaus, F.: Ueber eine seltene Form von Amyloid- und Hyalin-Infiltration am Circulations- und Digestionapparat, Ztschr. f. klin. Med. **45**:375, 1902.

In December 1944 the patient visited the gastrointestinal clinic complaining of anorexia, constipation and gaseous distention of the abdomen. Roentgenograms of the gastrointestinal tract were normal except for a questionable very small duodenal ulcer. Roentgenograms of the chest showed calcified bilateral hilar and left subapical tuberculosis with moderate thickening of the right apical pleura. On a low residue, nonlaxative diet and antispasmodic drugs the patient felt somewhat improved. However, he visited the psychiatry clinic in November 1945, with additional complaints: insomnia, impotence, loss of 30 pounds (13.6 Kg.) in one year and hypersensitivity of the skin to touch and clothing from the neck down. The hypersensitivity was such that the patient wore long underwear twenty-four hours a day to prevent any friction between his skin and his clothes. Associated with the hypersensitivity were "shooting pains" in the lower legs which kept him awake at night, and about which he complained bitterly. An excellent psychiatric explanation for his symptoms was elicited, and the diagnosis was neurotic depression at that time.

In March 1946 the patient began to have edema of the lower extremities, which slowly progressed to involve the sacral area and was accompanied by slight abdominal distention and a mild cough productive of small amounts of sputum, which was occasionally blood streaked.

Laboratory findings had been normal until May 1944, when a urinalysis revealed a slight trace of albumin. A subsequent specimen of urine was normal, but in November 1945, albumin was present (1 plus). On July 5, 1946, there were a few hyaline casts and 0.8 Gm. of albumin per hundred cubic centimeters. The serum albumin at this time was 3.05 Gm. per hundred cubic centimeters and globulin 1.84 Gm. A urea clearance in December 1945 had been 70 by the square root formula. His basal metabolic rate in November 1945 was normal.

*Examination.*—On physical examination, the patient looked chronically ill. There were a few small purpuric spots over the anterior part of the chest just below the clavicles. The eyes were somewhat prominent, but the extraocular movements were normal, and there was no lid lag. The retinal arterioles were generally narrow; the veins were not unusual. The tongue appeared normal. There was no lymphadenopathy. The chest was clear except for signs of fluid at both bases. The heart was not enlarged, the rhythm was regular, and there were no murmurs. The heart sounds were distant. The liver was palpable 5 cm. below the xiphisternum; the edge was smooth and not tender. The abdomen was moderately distended, and shifting dulness was present. Edema of the ankles was marked, it was slight in the thighs, and there was a moderate amount of edema of the sacral area. There was generalized hyperesthesia, most pronounced over the trunk anteriorly and on the volar surfaces of the arms. There was definite loss of pain and temperature sensation over the anterolateral aspect of the lower legs and, to a lesser degree, over the anterior aspect of the thighs. There was some loss of temperature sense in the same areas. Light touch sensation was normal, as was position sense. The patellar reflexes were greatly diminished, and the achilles reflexes were absent.

Studies of the blood showed 3,630,000 to 4,410,000 red blood cells, 12.5 to 13.7 Gm. of hemoglobin, and 5,050 to 8,400 white blood cells, with a differential count of 66 neutrophils, 32 lymphocytes, 2 monocytes and no eosinophils or basophils. The hematocrit value was 43 and the sedimentation rate 4 mm. per hour. Platelet counts were 170,000 and 227,000. Aspiration of the sternum revealed a normal marrow. The specific gravity of the urine was as high as 1.034 with albumin (3 plus) and occasional hyaline casts. The results of the Kahn and Wassermann tests of the blood were negative. Benzidine tests of four stools for

blood gave negative results, and they did not contain parasites or pathogenic organisms. Tubercle bacilli were not found in the sputum on direct examination or on inoculation into guinea pigs. The urea nitrogen and nonprotein nitrogen of the blood were normal until terminally. Urea clearances were 81 and 56 per cent of normal. Total serum lipids were 687 to 757 mg. per hundred cubic centimeters, total serum cholesterol 178 to 220 mg., cholesterol esters 110 to 155 mg. Total plasma proteins varied between 6.03 and 4.36 Gm. per hundred cubic centimeters; the plasma albumin was 3.61 to 2.92 Gm., plasma globulin 2.42 to 1.38 Gm. The lower figures were obtained the day before death. Plasma fibrinogen levels were 0.13, 0.14, and 0.15 Gm. per hundred cubic centimeters. Prothrombin times were 93, 100 and 78 per cent of normal. Serum bilirubin values were normal. Results of two thymol turbidity tests were negative and one plus; of cephalin flocculation tests, one and two plus. A sulfobromophthalein test showed no retention after thirty minutes. A congo red test showed 45 per cent retention by the tissues after sixty minutes; none was excreted in the urine. Bleeding time was four minutes; clotting time twelve minutes (capillary tube method). A tourniquet test for increased capillary fragility gave negative results.

*Treatment and Course.*—After the patient had been hospitalized for a little more than a month, it was found that each day he was passing two or three bulky, soft, grayish stools with a sheen. A three day collection while his food intake was constant, including 100 Gm. of fat per day, showed the stools to be 28 per cent fat, dry weight. Lipid fractions were not studied. Serum calcium content at this time was 4.2 mg. per hundred cubic centimeters. Part of the blood sample was lost, and the serum phosphorus could not be accurately determined; it was approximately 4 mg. per hundred cubic centimeters. After treatment with viosterol (2,640 units of vitamin D per day) and calcium (2.4 Gm. of dicalcium phosphate and 1.6 Gm. of calcium gluconate per day) for two days, the serum calcium was 6.1 mg. per hundred cubic centimeters, and the serum phosphorus 4.6 mg. Values terminally, by which time renal failure had supervened, administration of viosterol and calcium being continued, were calcium 8.2 mg. and phosphorus 9.3. An oral glucose tolerance test was flat, the highest blood glucose value being 93 mg. per hundred cubic centimeters. Lumbar puncture produced clear fluid containing 7 white blood cells and 43 mg. of protein per hundred cubic centimeters. The reaction to the Wassermann test was negative; the colloidal gold curve was 1111120000. The Pandy test gave a negative result. The initial pressure was 340 mm.; the final pressure was 260 mm. after 12 cc. had been removed. The dynamics were normal.

Roentgenograms of the chest demonstrated bilateral pleural effusion. The heart was not enlarged. On fluoroscopy, the cardiac pulsations appeared small. No pericardial calcification was seen. Roentgenograms of the gastrointestinal tract were normal except for displacement of the stomach and colon by the enlarged liver. Two electrocardiograms showed small QRS complexes and low T waves. Venous pressures were 18.5, 19.0, and 14.4 cm. of isotonic sodium chloride solution. The arm to tongue circulation time was forty-five seconds.

Because it was felt that the patient probably had constrictive pericarditis, attempts were made to prepare him for pericardiectomy. To this end, he was given infusions of "amigen" and plasma, but because thrombophlebitis of most of the superficial veins of both arms developed, the intravenous therapy had to be interrupted. He was able to take only small portions of the high carbohydrate, high protein, salt-poor diet that was offered him. His response to diuretic drugs was poor. The heart rate was usually 90 to 110.

On the twenty-second day in the hospital, a hemorrhage of the right sclera was noted. On the following day there was a hemorrhage into the left eyelid. At the same time an increase in the number of purpuric spots over the trunk anteriorly occurred. These did not exceed 3 mm. in diameter. On the fifty-ninth day a paracentesis was done, 2,900 cc. of yellow, slightly turbid fluid with a specific gravity of 1.009 and a protein content of 1.91 Gm. per hundred cubic centimeters being removed. Because of the persistent thrombophlebitis, plasma was given intrasternally. On the sixtieth day 1,500 cc. were given by this route. Late that night signs of mild vascular collapse developed. During the next week the blood pressure was only occasionally obtainable, at about 75 systolic and 65 diastolic. The patient became oliguric and progressively more edematous. He died on the sixty-eighth day in the hospital.

*Postmortem Findings.*—The autopsy was begun two and one-half hours after death. It was performed by Dr. J. R. Tobin Jr. and Dr. E. M. Humphreys. The body was that of an emaciated, edematous white man. The tongue and oral mucous membranes appeared normal. There was pitting edema extending from the feet to the axilla. The abdominal cavity contained 3,600 cc. of reddish yellow fluid. There were 1,300 cc. of bloody fluid in pockets between firm fibrous adhesions in the right pleural cavity. The medial surface of the right lung was densely adherent to the mediastinum. The left pleural cavity contained 800 cc. of serous fluid. The right lung weighed 450 Gm., the left 360 Gm. They were firm and subcrepitant. The pleural surfaces were covered with fine fibrous adhesions. There were antemortem thrombi in the radicles of the pulmonary arteries. The pericardial cavity contained 200 cc. of serous fluid. The pericardial surface was opaque and covered with minute yellow-gray granules. The heart weighed 580 Gm. All chambers had thick walls and prominent trabeculae carneae and papillary muscles. The mural endocardium was opaque and studded with yellowish semitranslucent granules. Similar granules were scattered over the cusps of the valves, making them moderately thick and stiff. They were more numerous on the valve leaflets but extended onto the chordae tendineae. All valves were similarly involved. The large coronary arteries were patent. Their intimas were wrinkled and covered with fine semitranslucent granules. This was also true of the intimas of the aorta, pulmonary arteries and venae cavae. The liver appeared small but weighed 1,600 Gm. The capsular surface was opaque and covered with fibrous adhesions. The cut surfaces were of nutmeg appearance, firm and rubbery. The spleen weighed 560 Gm. Its cut surfaces were dry, pink-red and glassy. There was infarction of the cecum and partial infarction of the left kidney. The ileocolic vein was thrombosed. No further abnormalities were found on gross examination of the gastrointestinal tract, kidneys or lymph nodes. The central nervous system was not examined.

By the application of iodine solution and sulfuric acid, amyloid was demonstrated grossly, the substance staining a deep golden brown with iodine and a reddish brown after the addition of acid. It was found in abundance in the myocardium, endocardium and epicardium; the intimas of the aorta and pulmonary arteries; the vessels and connective tissue of the portal triads of the liver; the serosa and blood vessels of the esophagus; the blood vessels of the stomach, intestines and spleen; tunica albuginea of the testes; areolar tissue; serous membranes in general, and in all blood vessels examined. The amyloid also stained with congo red, but the absorption was delayed.

Microscopically, amyloid was seen to be uniformly and selectively deposited in areolar tissue, blood vessels (subintimal and medial deposition), nerves and ganglions and collagenous connective tissue.

There was uniform and massive deposition of amyloid in the myocardium (fig. 1). It seemingly encased fibers, producing widespread atrophic and degenerative changes. It was deposited in small nodules in the endocardium of the ventricles and valves. The epicardial fat, vessels and nerves were similarly involved.

There was evidence of an old tuberculous process in one section of the right lung and in the apex of the left, but there was no evidence of active tuberculosis. There were thick hyaline calcified nodules in the right lung and a hyaline apical scar in the left. Amyloid was deposited in the septums of the lung, hyaline scars and alveolar walls, as well as in blood vessels.

There was massive amyloidosis of the spleen. Foreign body giant cells were present about the amyloid infiltrates.

The following organs contained moderate amounts of amyloid tissue: the adrenals; the entire gastrointestinal tract from esophagus to anus, chiefly in the muscularis mucosae and muscular coat, but also in the villi; and the kidneys, the amyloid being in the glomerular tufts, and, to a lesser degree, in the tubules.

There was heavy and uniform deposition of amyloid in the nerve trunks and perineural connective tissue at the root of the mesentery and in the celiac plexus (fig. 2). All recognizable ganglions contained amyloid.

It was also deposited about nerves, blood vessels and connective tissue of the liver, pancreas (which was also the site of intralobular fibrosis and acinar atrophy), thyroid, urinary bladder, prostate, seminal vesicles, tunica albuginea of the testes, skin, tongue and buccal mucous membranes.

There were small amounts in skeletal muscle fibers, the greatest amount being in their tendinous connections.

Amyloid was not found in the bone marrow; the maturation of blood elements was normal.

## COMMENT

When amyloid is deposited in the tongue, skin or lymph nodes in such a manner as to produce gross changes, the diagnosis should be readily established by biopsy. Enlargement of the tongue has been noted in 20 patients with this disease and was an important presenting complaint in 16 of them in whom the enlargement was so marked that dysarthria with or without dysphagia was present.[2] Amyloid deposits have been observed grossly in the skin of 11 patients with primary systemic amyloidosis. They have produced lesions described as sclerodermic,[3] papular, eczematous,[4] opalescent, firm and nodular.[5] Enlarge-

2. Eisen, H. N.: Primary Systemic Amyloidosis, Am. J. Med. **1**:144 (Aug.) 1946.

3. (a) Lubarsch, O.: Zur Kenntnis ungewöhnlicher, Amyloidablagerungen, Virchows Arch. f. path. Anat. **271**:867 (March 20) 1929. (*b*) Gerstel, G.: Ueber atypische Lokalisation des Amyloids insbesondere über die Makroglossia amyloides diffusa, ibid. **283**:466 (Feb. 5) 1932. (*c*) Gaupp, A.: Ein Fall von generalisierter, atypischer Amyloidose (Paramyloidose), Düsseldorf, G. H. Nolte, 1934.

4. Lindsay, S., and Knorp, W. F.: Primary Systemic Amyloidosis, Arch. Path. **39**:315 (May) 1945.

5. Mollow, W., and Lebell, H.: Zur Klinik der systematisierten Amyloidablagerung, Wien. Arch. f. inn. Med. **22**:205, 1932.

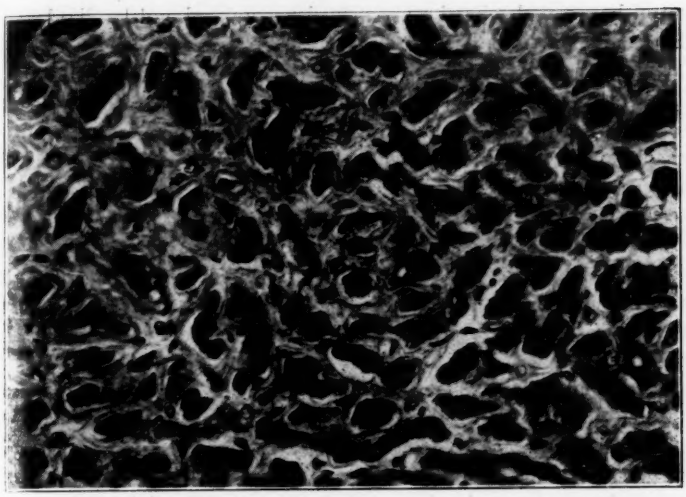

Fig. 1.—Heart; hematoxylin and eosin stain. The interstitium consists chiefly of amyloid, which encases fibers and is associated with atrophy and degeneration, but not with necrosis. × 292.

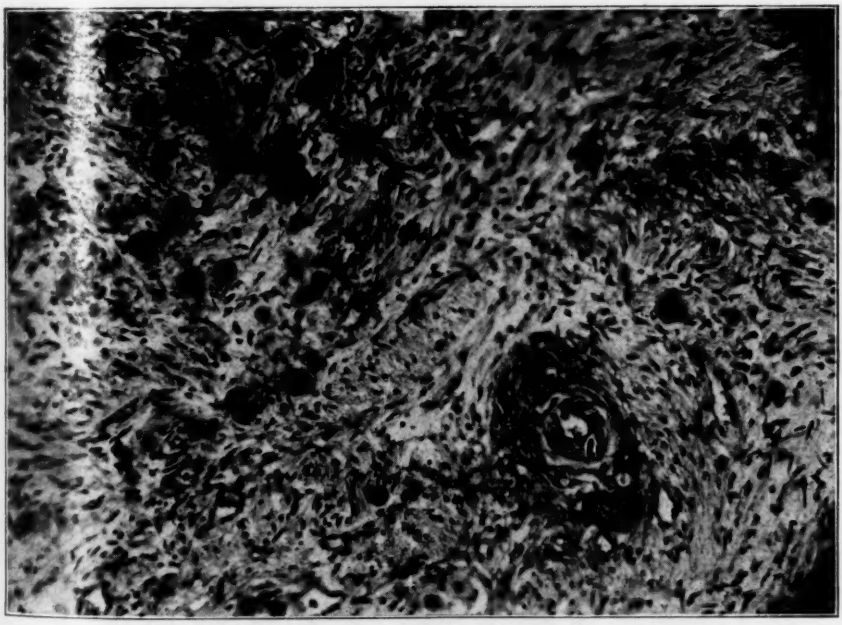

Fig. 2.—Celiac ganglions; hematoxylin and eosin stain. Amyloid surrounds the blood vessel to the right of and below the center. It is also deposited indiscriminately throughout the slide, appearing as poorly defined masses and sharply defined, roughly circular darker areas. × 138.

ment of lymph nodes has been reported generalized and localized in the form of amyloid tumors.[4]

Unless these external changes are present, the diagnosis is apt to be difficult. The congo red test has been done in 12 of the reported cases and was equivocal or negative in 6 of them. Involvement of skeletal muscle has been noted in 19 cases. Thus, a specimen of a muscle for biopsy may be diagnostic if the possibility of this disease is entertained. Such a procedure would have established the nature of the illness in the reported case.

Dirske [6] has recently discussed the roentgen findings in the chest reported in primary systemic amyloidosis and suggests that further observations may show them to be of some diagnostic value when the disease happens to involve the mediastinum and lungs.

The combination of elevated venous pressure, prolonged circulation time, low pulse pressure, small cardiac movements on fluoroscopy, low electrocardiographic voltage, hepatomegaly, decreased serum albumin with a normal concentration of globulin, albuminuria, dependent edema and ascites led to a diagnosis of constrictive pericarditis. The bizarre generalized hypersensitivity of the skin to touch was believed to be due in part to a peripheral neuropathy and in part a neurotic manifestation. The low plasma fibrinogen and prolonged bleeding time were not satisfactorily explained. Steatorrhea has been observed in constrictive pericarditis [7] and also in amyloidosis.[8]

It is not surprising that deposition of amyloid in the heart should simulate constrictive pericarditis. In both diseases the normal contraction and relaxation of the chambers is precluded, in the one disease by confinement of the individual muscle fibers and in the other by confinement of the organ as a whole. However, in none of the previously reported cases was constrictive pericarditis diagnosed, and in only a small proportion of the cases were the findings suggestive of this disease. Fifty-two per cent (28) of the patients had edema; 30 per cent (16) had hydrothorax; 28 per cent (15) had ascites. In addition to the reported case, one venous pressure (3) and no circulation times or appearances of cardiac action of fluoroscopy are recorded. Since Lindsay's survey [9] of 45 cases of primary systemic amyloidosis, which included

6. Dirske, P. R.: Primary Amyloidosis of the Lungs, Am. J. Roentgenol. **56**:577 (Nov.) 1946.

7. Clemmesen, J.: Steatorrhea Arthro-Pericarditica (Mesenteric Chyladenectasis): Review and Report of a Case, Acta med. Scandinav. **121**:495, 1945.

8. Schein, J.: Syndrome of Non Tropical Sprue with Hitherto Undescribed Lesions of the Intestine, Gastroenterology **8**:438 (April) 1947. Adlersberg, D., and Schein, J.: Clinical and Pathologic Studies in Sprue, J. A. M. A. **154**:1459 (Aug. 23) 1947.

9. Lindsay, S.: The Heart in Primary Systemic Amyloidosis, Am. Heart J. **32**:419 (Oct.) 1946.

electrocardiograms in 12 cases, 6 of these showing low voltage, 9 additional cases have been reported.[10] Electrocardiograms were made in all of these, and 7 showed low voltage. Thus, of the total of 21 electrocardiograms which have been reported, 13 have shown low voltage.

One of the most interesting and unusual features of this case was the spectacular involvement of the nerves with the attendant symptoms. Similarly distributed deposits have been reported by DeNavesquez and Treble[10b] and by Götze and Krücke.[11] These patients complained of muscular weakness, paralyses, incontinence, impotence, paresthesias and various other neurologic disturbances. Ganglions and peripheral nerves were strikingly involved in both cases, and the patient of Götze and Krücke also had extensive deposits in blood vessel walls throughout the brain substance.

Purpura has been seen in 10 cases. It has been attributed to amyloid deposition in cutaneous blood vessels,[1] but, as has been remarked by Eisen,[2] this explanation is not satisfactory, for perivascular hemorrhages do not occur elsewhere. In any event, it is difficult to understand why the skin should be involved exclusively. Epistaxis and bleeding ulcers of the skin have been found.[4] The plasma fibrinogen in the reported case was not low enough to produce hemorrhagic manifestations per se, although it is perhaps conceivable that it in combination with increased venous pressure and low serum calcium was instrumental. No abnormalities of the clotting mechanism have been reported previously. Massive gastrointestinal bleeding has been described,[12] but this was apparently due to changes in the mucosa rather than changes in the blood.

It is stated in the protocol of one of these cases,[12b] in which there was marked amyloidosis of the gastrointestinal tract, that the patient "had frequent foul-smelling light yellow stools . . ." As in the subject of the present report, steatorrhea may have been present.

Two cases of amyloidosis involving the small intestine have recently been reported.[8] It has been suggested that amyloid disease may be

10. (*a*) Eisen.[2] (*b*) De Navesquez, S., and Treble, H. A.: Case of Primary Generalized Amyloid Disease with Involvement of Nerves, Brain **61**:116 (March) 1938. (*c*) Soisalo, P., and Ritama, V.: Atypical Amyloidosis with Special Consideration of Heart, Acta med. Scandinav. **116**:260, 1944. (*d*) Orloff, J., and Felder, L.: Primary Systemic Amyloidosis: Jaundice as a Rare Accompaniment, Am. J. M. Sc. **212**:275 (Sept.) 1946. (*e*) Atkinson, A. J.: Clinical Pathological Conference, Gastroenterology **7**:477 (Oct.) 1946. (*f*) Zemp, F. E.: Primary Amyloidosis, Ann. Int. Med. **26**:448 (March) 1947.

11. Götze, W., and Krucke, W.: Ueber Paramyloidose mit besonderer Beteiligung der peripheren Nerven und granulärer Atrophie des Gehirns, Arch. f. Psychiat. **114**:183 (Nov. 7) 1941.

12. (*a*) Lubarsch.[3a] (*b*) Golden, A.: Primary Systemic Amyloidosis of the Alimentary Tract, Arch. Int. Med. **75**:413 (June) 1945.

found to be an important cause of the sprue syndrome if the intestinal tracts of such patients are examined with this in mind.

This patient lived about two years after the onset of his symptoms, a somewhat shorter period than the average of thirty-two months found by Eisen.[2]

There is some reason to associate amyloidosis with an abnormality of one or more of the serum globulins. Reimann, Koucky and Eklund [13] gave 4 rabbits approximately ninety-three intramuscular injections of sodium caseinate over a period of eight to thirteen months. During this time the amount of blood globulin was increased from two to four times over the normal level. Each of the animals died from extensive amyloid disease. Kuczynski [14] produced amyloid disease in mice simply by feeding large amounts of casein. Dick and Leiter [15] noted hyperglobulinemia in association with the amyloidosis produced in rabbits by the use of various strains of streptococci. Reimann and Eklund have noted that the secondary form of amyloidosis occurs in diseases in which hyperglobulinemia is frequently present. They report a case [16] in which forty-one injections of bacterial vaccine were given at more or less regular intervals over a period of twenty-two months. Postmortem examination revealed extensive amyloidosis of the spleen, liver, kidneys and adrenals. Their patient also had chronic arthritis, which may have been an important factor in the cause. Shortly after death the blood proteins were 4.7 Gm. per hundred cubic centimeters, composed of 1.29 Gm. fibrinogen, 2.67 Gm. globulin and 0.74 Gm. albumin. Serum globulins have been noted to fall rather strikingly in patients with multiple myeloma when amyloidosis developed.[17] Our patient's serum globulin fell very late in the course; it is difficult to attach much significance to this. This patient had pollen vaccine therapy for fall pollen disease, but large numbers of patients receive similar therapy without development of amyloidosis. No history of allergy was encountered by Eisen in his collection of 48 cases.[2]

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13. Reimann, H. A.; Koucky, R. F., and Eklund, C. M.: Primary Amyloidosis Limited to Tissues of Mesodermal Origin, Am. J. Path. **11**:977 (Nov.) 1935.

14. Kuczynski, M. H.: Edwin Goldmanns Untersuchungen über cellulare Vorgänge im Gefolge des Verdauungsprozesses auf Grund nachgelassener Präparate dargestellt und durch neue Versuche ergänzt, Virchows Arch. f. path. Anat. **239**: 185, 1922.

15. Dick, G. F., and Leiter, L.: Experimental Amyloidosis and Hyperglobulinemia, Tr. A. M. Physicians **52**:246, 1937.

16. Reimann, H. A., and Eklund, C. M.: Long Continued Vaccine Therapy as a Cause of Amyloidosis, Am. J. M. Sc. **190**:88 (July) 1935.

17. Tarr, L., and Ferris, H. W.: Multiple Myeloma Associated with Nodular Deposits of Amyloid in Muscles and in Joints, Arch. Int. Med. **64**:820 (Oct.) 1939. Chester, W.: Multiples Myelom und Hypoproteinämie, Ztschr. f. klin. Med. **124**: 466, 1933. Freeman, I., and Krause, L. A. M.: Multiple Myeloma with Localized Amyloid Deposits, Bull. School M. Univ. Maryland **26**:7 (Oct.) 1941.

SUMMARY

A case of primary systemic amyloidosis is presented. Interesting features of the case include its clinical resemblance to constrictive pericarditis, the occurrence of steatorrhea, hypocalcemia, a tendency to bleed and the presence of neural involvement by the amyloid substance.

The diagnosis is difficult in the absence of a positive congo red test or certain common external manifestations, such as involvement of the skin, lymph nodes or tongue; it was not made before death in this case. Biopsy of muscle might have made the diagnosis possible.

The combination of elevated venous pressure, low pulse pressure, small cardiac movements, low electrocardiographic voltage, hepatomegaly, low serum albumin with normal globulin, albuminuria, dependent edema and ascites led to a diagnosis of constrictive pericarditis. Most of these findings have been noted in primary amyloidosis before. Cardiac inactivity and prolonged circulation time have not been previously reported. Elevation of venous pressure has been noted once.

The occurrence of steatorrhea and hypocalcemia is of interest in connection with a recent suggestion that amyloidosis may occasionally cause the sprue syndrome.

Unexplained bleeding was present and has been noted in other cases.

While neural involvement has been reported twice, neither patient had the exquisite cutaneous hypersensitivity found in this case.

# STUDIES ON HYPERTENSION

## VII. Mechanism of the Fall in Arterial Pressure Produced by High Spinal Anesthesia in Patients with Essential Hypertension

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HIGH spinal anesthesia was employed in previous studies[1] to lower the blood pressure of patients with essential hypertension. From these studies certain information and conclusions have been drawn regarding the probability that the drop in blood pressure is due to interruption of vasomotor function.

The work of Smith and his associates[2] and Rovenstine and his associates[3] suggested that the fall in blood pressure due to spinal

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1. Gregory, R.; Lindley, E. L., and Levine, H.: Studies on Hypertension: I. The Effect on the Renal Function of Decreasing the Blood Pressure of Patients with Hypertension, Tex. Rep. Biol. & Med. **1**:59-76, 1943; II. The Effect of Spinal Anesthesia on the Blood Pressure of Hypertensive Patients: Its Possible Bearing on the Pathogenesis of Essential Hypertension, ibid. **1**:167-206, 1943. Gregory, R.; Levine H., and Lindley, E. L.: Studies on Hypertension: III. The Site of Action of Angiotonin; the Pressor Effects of Angiotonin on Patients Having Essential Hypertension, and Possible Relationship to the Pathogenesis of Essential Hypertension, ibid. **2**:121-134, 1944. Gregory, R.; Ewing, P. L.; Levin, W. C., and Ross, G. T.: Studies on Hypertension: IV. Bioassay of Vasoconstrictor Substances in Ultrafiltrates of Citrated Blood Plasma from Patients with Normal Blood Pressures, Patients with Essential Hypertension and Patients Made Hypertensive by Intravenous Injections of Angiotonin (Hypertension), Arch. Int. Med. **76**:11-21 (July) 1945. Gregory R., and Levin, W. C.: Studies on Hypertension: V. Effect of High Spinal Anesthesia on the Blood Pressure of Patients with Hypertension and Far-Advanced Renal Disease—Its Possible Relationship to the Pathogenesis of Hypertension, J. Lab. & Clin. Med. **30**:1037-1043, 1945. Gregory, R.; Levin, W. C.; Ross, G. T., and Bennett, A.: Studies on Hypertension: VI. Effect of Lowering the Blood Pressure of Hypertensive Patients by High Spinal Anesthesia on the Renal Function as Measured by Inulin and Diodrast Clearances, Arch. Int. Med. **77**:385-392 (April) 1946.

2. Smith, H. W.; Rovenstine, E. A.; Goldring, W.; Chasis, H., and Ranges, H. A.: The Effect of Spinal Anesthesia on the Circulation in Normal, Unoperated Man with Reference to the Autonomy of the Arteriolar, and Especially Those of the Renal Circulation, J. Clin. Investigation **18**:319-341, 1939.

3. Rovenstine, E. A.; Papper, E. M., and Bradley, S. E.: Circulatory Adjustments During Spinal Anesthesia in Normal Man with Special Reference to the Autonomy of Arteriolar Tone, Anesthesiology **3**:421-428, 1942.

anesthesia is due to decreased cardiac output resulting from decreased venous pressure and diminished venous return to the heart. In view of the fact that both of these studies were done on subjects with normal blood pressure, it appears necessary that these observations be applied to patients with essential hypertension. It is conceivable that the role played by the vasomotor apparatus in maintaining normal blood pressure may be different from the role of this mechanism in maintaining elevations of arterial pressure in hypertension.

In the previous studies [4] no observations were made on venous pressures. The present study is the first of several devised to elucidate the mechanism of the fall of arterial pressure produced by spinal anesthesia in patients with essential hypertension.

The mechanism of the fall of arterial pressure during spinal anesthesia has engaged the attention of a number of workers. In general, the studies have been concerned with whether there is a decrease in cardiac output, and, if so, whether this is causally related to the fall in arterial pressure.

Burch and Harrison [5] studied the effect of spinal anesthesia on the cardiac output of dogs. They showed that the fall in arterial pressure produced the fall in cardiac output in some instances, and in most instances the degree of fall in arterial pressure was disproportionately greater than the fall in cardiac output. They concluded that the initial change is in the arterial pressure and that the venous return and cardiac output are affected secondarily.

Ferguson and North [6] have emphasized, in a study on dogs, the slight role that splanchnic dilatation plays in the fall of arterial pressure during spinal anesthesia. But they have further demonstrated the essential part played by the general vasomotor paralysis in the fall of arterial pressure induced by spinal anesthesia.

By plethysmographic studies on a finger and a toe, Neumann, Foster and Rovenstine [7] have stressed the importance of compensating vasoconstriction in unanesthetized areas in the maintenance of blood pressure during spinal anesthesia.

Sarnoff and Arrowood [8] have made an important contribution to the understanding of the effects of spinal anesthesia on blood pressure.

4. Smith and others.[2] Rovenstine, Papper and Bradley.[3]

5. Burch, J. C., and Harrison, T. R.: The Effect of Spinal Anesthesia on the Cardiac Output, Arch. Surg. **21**:330-332 (Aug.) 1930.

6. Ferguson, L. K., and North, J. P.: Observations on Experimental Spinal Anesthesia, Surg., Gynec. & Obst. **54**:621-634, 1932.

7. Neumann, C.; Foster, A. D., Jr., and Rovenstine, E. A.: The Importance of Compensating Vasoconstriction in Unanesthetized Areas in the Maintenance of Blood Pressure During Spinal Anesthesia, J. Clin. Investigation **24**:345-351, 1945.

8. Sarnoff, S. J., and Arrowood, J. G.: Differential Spinal Block, Surgery **20**:150-159, 1946.

They have shown that "differential spinal block" with low concentrations of procaine hydrochloride in patients with normal blood pressure may produce significant falls in arterial pressure in spite of an absence of paralysis of skeletal muscle. From the lack of paralysis of skeletal muscle, they have concluded that there was no decrease in venous return and, consequently, no decrease in cardiac output.

## METHOD OF STUDY

The venous and arterial pressures were simultaneously recorded at one-half to two minute intervals before, during and following recovery from high spinal anesthesia. The technic of spinal anesthesia was that employed in our previous studies. Anesthesia uniformly reached the level of the fourth dorsal segment or higher—in most instances it was higher. These observations have been made in 5 patients with normal arterial pressures and twelve times in 10 patients with essential hypertension.

Simultaneous observations of arterial and venous pressures were made because it was thought that the time relationships between the changes in these values would be of some importance in arriving at conclusions regarding cause and effect relationships.

Arterial pressures were determined in the usual way with the cuff and mercury manometer. Venous pressures were measured with a water manometer, using 2.5 per cent of sodium citrate in isotonic solution of sodium chloride in the system. The needle was allowed to remain continuously in one of the antecubital veins. Precaution was always exercised to ascertain that the liquid in the water manometer registered respiratory oscillations.

Spinal puncture was accomplished in the conventional lateral recumbent position, with a malleable needle. The patient was then placed in the dorsal recumbent position. The position of the arm in which observations of venous pressures were made was fixed and its position to the axillary midline established so that the level of the vein and this line were the same, or, if different, the difference was recorded. After adequate control observations were made in this position, 150 mg. of procaine hydrochloride in 3 cc. of spinal fluid was rapidly injected intrathecally.

## RESULTS

Five patients with normal blood pressure were studied. Figure 1 (H: M.) demonstrates that the arterial pressure may fall before the venous pressure falls. The systolic pressure had fallen from 110 mm. of mercury to 94 mm. of mercury, while the venous pressure was above the control level. The recovery of both systolic pressure and venous pressure began about the same time. But the slope of the curve of the systolic blood pressure indicates a slightly more rapid recovery compared with the curve of venous pressure. It is important to note also that the diastolic pressure showed a significant drop from 64 to 52 mm. of mercury. We believe that this indicates a vasomotor influence in maintaining arteriolar tone even in patients with normal blood pressure. This is at variance with the work of Rovenstine, Papper and Bradley.[3]

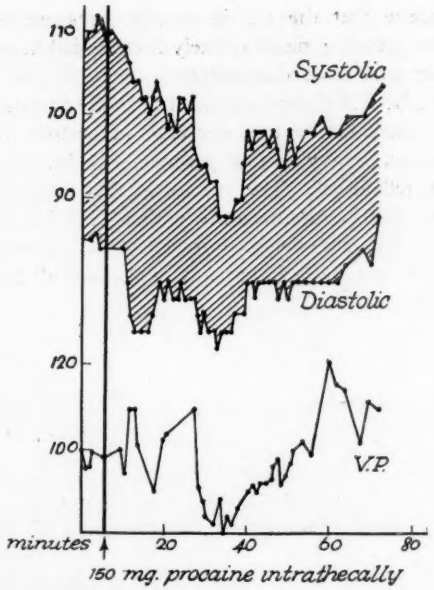


Fig. 1.—Graph of levels of blood pressure of patient H. M., demonstrating that arterial pressure may fall before the venous pressure falls.

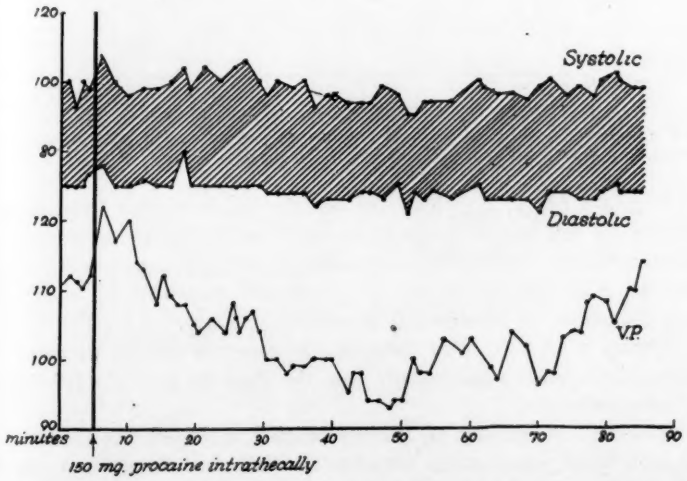


Fig. 2.—Graph of levels of blood pressure of patient L. D. K., demonstrating that venous blood pressure may fall significantly with no fall in arterial pressure.

We further believe that the fall in systolic pressure which preceded the fall in venous pressure makes it likely that the fall in arterial pressure is not due to decrease in cardiac output.

Figure 2 (L. D. K.) shows a decided decrease in venous blood pressure twenty minutes before any decrease in systolic blood pressure, which was slightly, if any, below preanesthetic levels. The diastolic pressure hardly fell at all. The results in this patient show that the venous pressure may fall significantly with no fall in arterial pressure.

Figure 3 (A. H.) also demonstrates that the venous pressure may fall an appreciable amount without any sustained fall in either systolic or diastolic pressures.

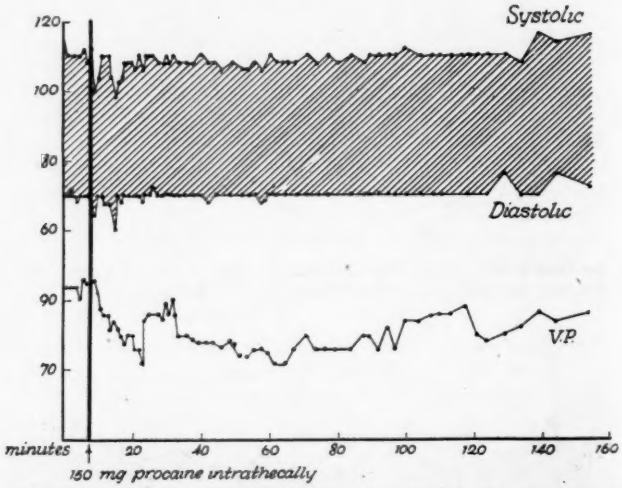


Fig. 3.—Graph of levels of blood pressure of patient A. H., demonstrating fall in venous pressure without any sustained fall in arterial pressure.

Figure 4 (J. T. J.) illustrates that the fall in venous pressure may precede the fall in systolic pressure but that the systolic pressure may continue to fall in spite of a progressive rise in the venous pressure. The diastolic pressure also shows a distinct and sustained fall coinciding with the period of greatest fall in systolic pressure.

Figure 5 (L. Y.) also demonstrates that the venous pressure fell before the arterial pressure and that the diastolic pressure fell during spinal anesthesia.

The limited number of 5 cases studied indicates that there is no constant time relationship between the falls in venous and arterial pressures produced by spinal anesthesia in patients with normal blood pressure. The venous pressure may fall first, or the arterial pressure may fall first.

It should be also noted that a fall in venous pressure is not necessarily associated with a fall in arterial pressure. Significantly, 3 of the normal persons showed falls in diastolic blood pressure. This point emphasizes

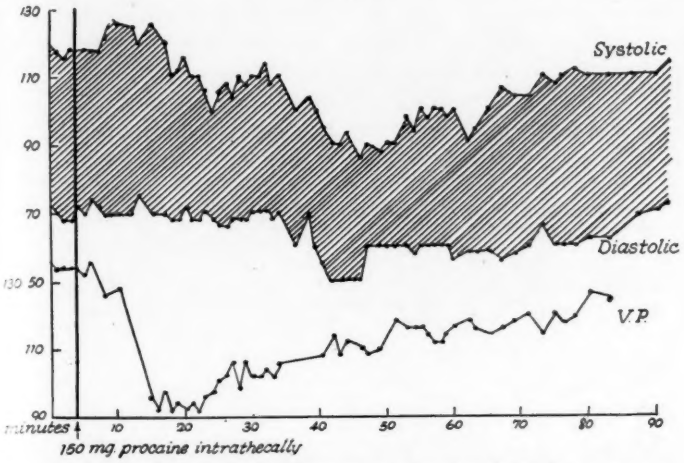


Fig. 4.—Graph of levels of blood pressure of patient J. T. J., showing a fall in venous pressure preceding the fall in systolic pressure.

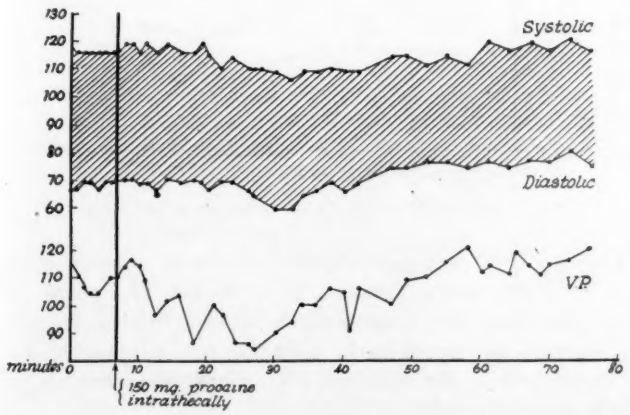


Fig. 5 (L. Y.).—Fall in venous pressure preceding the fall in arterial pressure.

the importance of the role that vasomotor function plays in maintaining normal arteriolar tonus.

According to the results, patients with hypertension may be divided into three groups: (*a*) those that showed a drop in venous pressure first with no significant drop in arterial pressure (two studies on 1

patient), (*b*) those showing a drop in arterial pressure first (7 patients) and (*c*) those showing a drop in venous pressure first, with a subsequent drop in arterial pressure (2 patients).

*Patients Showing First a Drop in Venous Pressure Without a Significant Drop in Arterial Pressure.*—This was shown to be the case in only 1 patient. Because no significant fall in arterial pressure occurred, the determination was repeated, with similar results. Figure 6, which is a graph of the first study on patient K, shows a fall in venous pressure

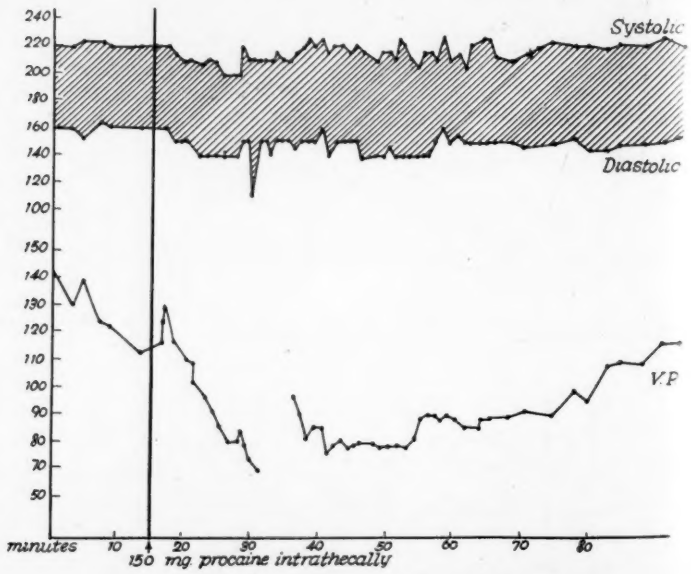


Fig. 6.—Graph of levels of blood pressure in patient K.

from a control level of about 115 mm. of isotonic solution of sodium chloride to 70 mm. and a sustained fall to 80 mm. of isotonic solution of sodium chloride. There was a slight fall in arterial pressure, which quickly returned to control levels while the venous pressure remained at the lowest level of the sustained fall. Figure 7 (patient K) shows practically identical results.

Although the falls in systolic and diastolic pressures were slight in both of these studies on patient K, we emphasize that there was a fall in diastolic as well as systolic pressure. In figure 7, the fall that occurred in systolic and diastolic pressure, about forty minutes after the induction of spinal anesthesia, was probably the result of casual change due to prolonged rest rather than to the spinal anesthesia.

*Patients Showing Falls in Arterial Pressure Before Falls in Venous Pressure.*—Figures 8 through 11 graphically present the data on 4

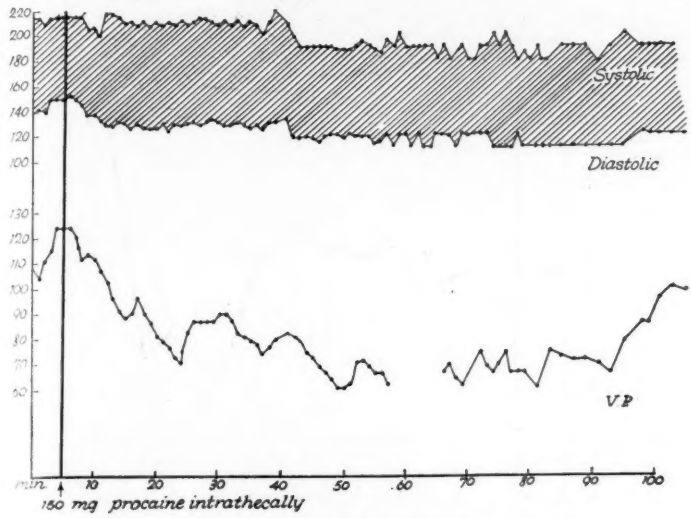


Fig. 7.—Graph of levels of blood pressure in patient K.

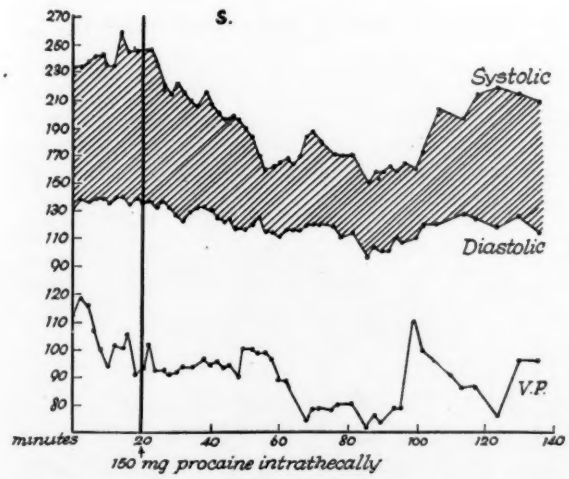


Fig. 8.—Graph of levels of blood pressure in patient S.

patients in whom the arterial pressure fell significantly before there was an appreciable drop in venous pressure.

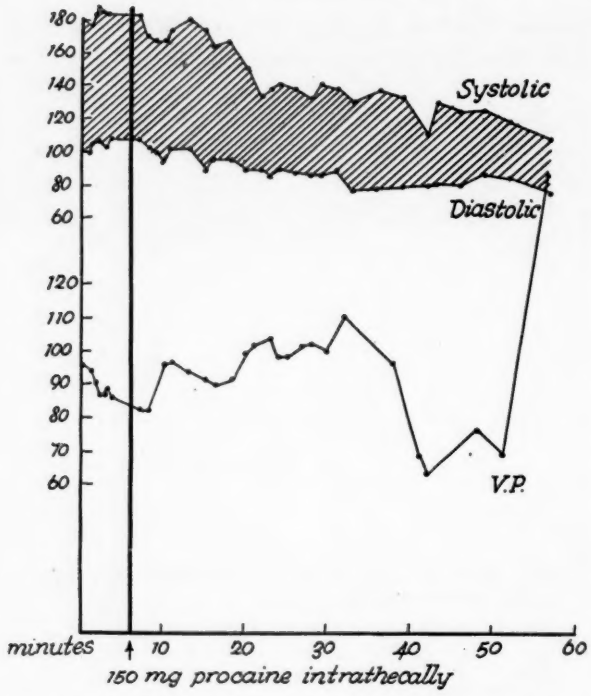


Fig. 9.—Graph of levels of blood pressure in patient J. L.

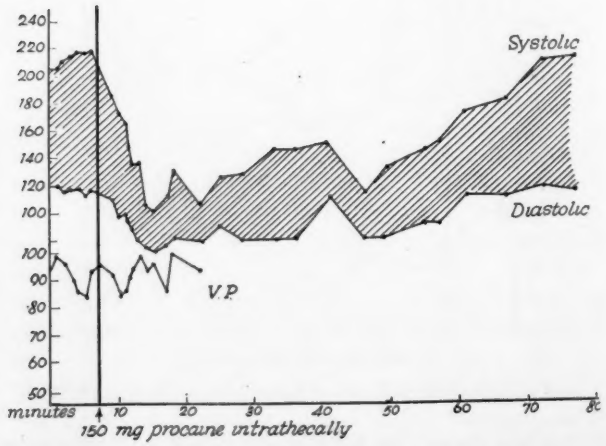


Fig. 10.—Graph of levels of blood pressure in patient B. J.

As in the previous group of patients, we feel that it is highly significant that there was a moderate or decided fall in the diastolic pressure. In a group of 7 patients the diastolic pressure dropped to

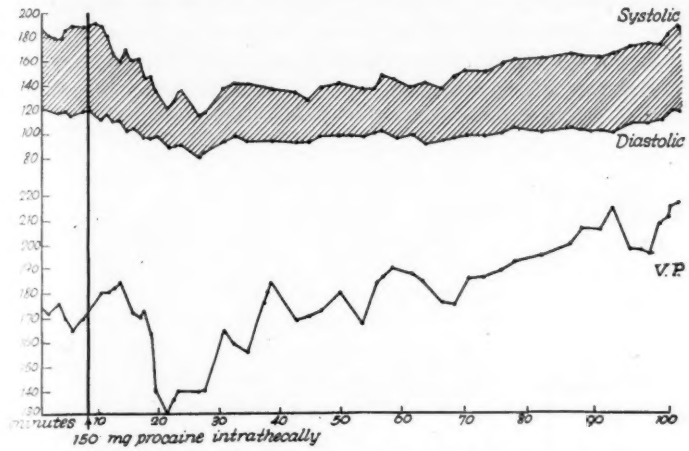


Fig. 11.—Graph of levels of blood pressure in patient H. M. C.

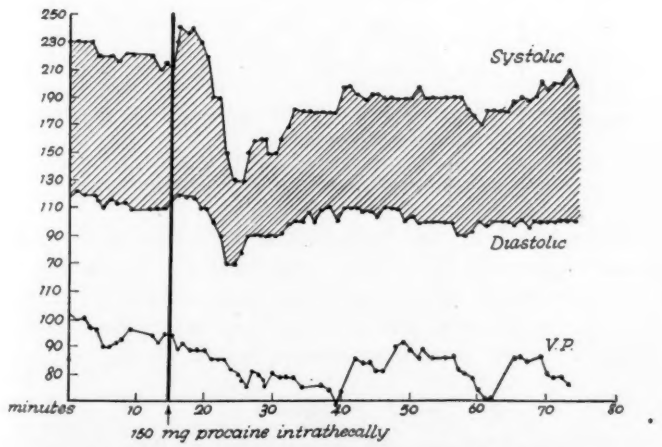


Fig. 12.—Graph of levels of blood pressure in patient D.

normal level in 5. The remaining 2 patients showed decided falls in diastolic pressure, but not to normal levels.

*Falls in Venous Pressure Before Arterial Pressure.*—There are only 2 patients who showed results which can be classified in this group.

The results on patient D (fig. 12) have been classified in this category, but the results are equivocal. While it is true that the venous pressure had begun to fall before the arterial pressure, both the systolic and the diastolic pressures fell to their lowest points before the venous pressure fell to its lowest level. It is also to be emphasized that the arterial pressure was rising while the venous pressure was falling. The venous pressure rose to control levels, while a significant drop in the arterial pressure was maintained.

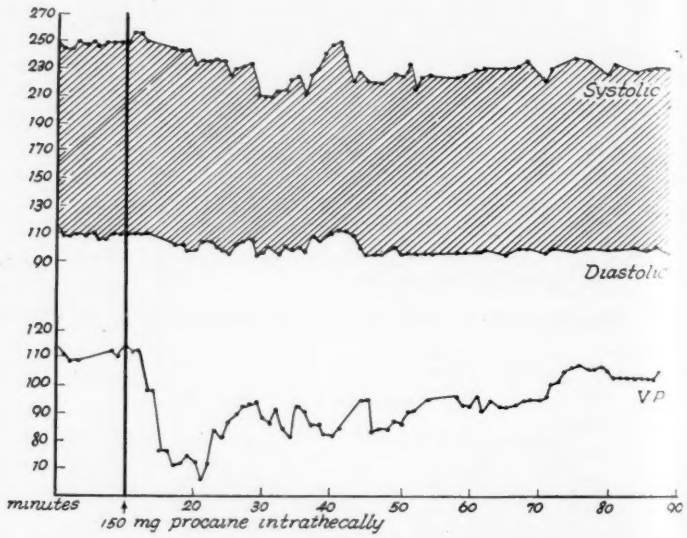


Fig. 13.—Graph of levels of blood pressure in patient F. F.

Figure 13 (F. F.) clearly shows that the venous pressure fell before the arterial pressure fell. On the other hand, the venous pressure rose significantly toward the control values, while the arterial pressure was continuing to fall to its lowest level. There was a small, and perhaps insignificant, drop in diastolic pressure in this patient.

## SUMMARY

Simultaneous arterial and venous pressures were determined in 5 normotensive subjects. Twelve separate studies were made in 10 patients with a clinical diagnosis of essential hypertension. Control observations were made, and similar determinations were then made with high spinal anesthesia induced by 150 mg. of procaine hydrochloride. Observations were continued during recovery stages.

## CONCLUSIONS

In the majority of patients with essential hypertension, the arterial pressure fell before the venous pressure fell. In 1 case, the venous pressure fell without any significant decrease in arterial pressure. In only 2 cases, the venous pressure dropped first, and in these 2 cases the arterial pressures fell to their lowest levels before the venous pressures fell to their lowest levels. In these 2 cases, the arterial pressures were rising while the venous pressures continued to fall.

There is no constant time correlation between the falls of arterial and venous pressures during high spinal anesthesia in patients with hypertensive disease. The changes in arterial and venous pressures described are probably not causally related.

It is extremely unlikely that decreased venous return and diminished cardiac output are the causes of the fall in arterial pressure caused by high spinal anesthesia in either normotensive or hypertensive subjects.

The failure of these data to support the idea that decreased cardiac output is the cause of falls in arterial pressure gives additional support to the likelihood that these falls in arterial pressure are caused by interruption of vasomotor function.

# EXOPHTHALMOS AND THIOURACIL THERAPY

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THE GREAT majority of patients with thyrotoxicosis and exophthalmos appear to have recession of the exophthalmos after a satisfactory subtotal thyroidectomy. However, careful observation of the eyes of these patients with exophthalmometer measurements made before and after thyroidectomy [1] reveals that this appearance is misleading. Actually the protrusion of the eyeballs increases after thyroidectomy in 75 [1a] to 97 per cent [1b] of the patients, but the disappearance of retraction of the lids and of associated eye signs gives the erroneous impression that the exophthalmos has been relieved.

It has been observed by Soley [1a] that progression of exophthalmos in patients with thyrotoxicosis was followed by intensification of the exophthalmos in 37 per cent fewer cases after roentgen therapy than after thyroidectomy. This decreased incidence was thought to be due to a slower return of the endocrine imbalance, present in thyrotoxicosis, to the normal balanced state. Since patients with thyrotoxicosis responded to thiouracil more slowly than to subtotal thyroidectomy,[2] it seemed worth while to analyze the results of exophthalmometer measurements on patients under treatment with thiouracil and propyl thiouracil.

Dobyns [1b] reviewed 11 cases in which patients with exophthalmic goiter were treated with thiouracil and followed carefully with exophthalmometric measurements. All patients experienced significant decrease in the basal metabolic rate and some increase in the prominence of the eyes ranging from 0.5 to 4.75 mm. Changes of less than 1 mm. were considered insignificant. However, 7 of the 11 showed progression of exophthalmos to the extent of 1.5 mm. or more.

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From the Department of Internal Medicine, University of Michigan.

1. (*a*) Soley, M. H.: Exophthalmos in Patients with Various Types of Goiter, Arch. Int. Med. **70**:206 (Aug.) 1942. (*b*) Dobyns, B. M.: The Influence of Thyroidectomy on the Prominence of the Eyes in the Guinea Pig and in Man, Surg., Gynec. & Obst. **80**:526, 1945. (*c*) Dobyns, B. M., and Haines, S. F.: Changes in the Prominence of the Eyes in Various Thyroid States, J. Clin. Endocrinol. **6**:633 (Oct.) 1946. (*d*) Rundle, F. F., and Wilson, C. W.: Development and Course of Exophthalmos and Ophthalmoplegia in Grave's Disease, with Special Reference to the Effect of Thyroidectomy, Clin. Sc. **5**:177, 1945.

2. Beierwaltes, W. H., and Sturgis, C. C.: Thiouracil and Propyl Thiouracil: A Comparative Clinical Study, J. Lab. & Clin. Med. **32**:392 (April) 1947.

## MATERIAL AND METHODS

One hundred and ninety-two exophthalmometer measurements were made for 28 successive patients with thyrotoxicosis under treatment with either thiouracil or propyl thiouracil. In addition one hundred and fourteen measurements were made for 12 patients with malignant exophthalmos. In 7 of the latter group the condition was toxic, and they were treated with thiourea derivatives alone, while the remaining 4, whose condition resembled the dissociated type of ophthalmopathy described by Hertz and Means,[3] were treated with both Lugol's solution and desiccated thyroid. One observer made over 75 per cent of all measurements. The readings were made usually at weekly intervals, on the same day each week, at 3 to 4 p. m. with a Hertel exophthalmometer. A single interocular distance was recorded for each patient, and care was used to have the eyes in the same vertical and horizontal positions at each recording. Each reading was made without reference to the previous reading.

## RESULTS

*Thyrotoxicosis Without Malignant Exophthalmos.*—Twenty-two of the 28 patients in this group were women, or 78 per cent. The age varied from 15 to 59 years, the average being 41 years. During the period of observation in which exophthalmometer readings were made, the basal metabolic rate fell an average of 20 per cent, with a corresponding change in the patient's clinical condition, including changes in the weight, pulse, pulse pressure and plasma cholesterol level. The period of observation averaged four months, with 21 patients followed for two or more months, 4 followed for nine or more months and 2 followed for seventeen months each. There was no significant change in the exophthalmometer readings during this time, the average change being an increase of 0.4 mm. for each eye. The minimum change considered significant is 1 mm.[1a] Three patients in this group had significant changes in the right eye, and 4 had them in the left eye. The changes in the right eye consisted of an increase of over 1 mm. in 1 patient and a decrease of over 2 mm. in 2 patients. In the left eye the changes were an increase of over 1 mm. in 2 patients and a decrease of over 1 mm. in 2.

*Malignant Exophthalmos.*—Criteria for the presence of "malignant exophthalmos" consisted of the presence of one or more of the following signs in patients with thyroid disease with exophthalmos: edema of lids, edema of conjunctiva with injection and corneal ulceration.

As would be expected,[4] males were in the majority, forming 64 per cent of the total. The average age was 33 years in this group of 11 patients. In 6 of the patients the condition was toxic, the basal metabolic

3. Hertz, S.; Means, J. H., and Williams, R. H.: Graves' Disease with Dissociation of Thyrotoxicosis and Ophthalmopathy, West. J. Surg. **49**:493 (Sept.) 1941.

4. Mulvaney, J. H.: Exophthalmos of Hyperthyroidism: Differentiation in Mechanism, Pathology, Symptomotology, and Treatment of Two Varieties, Am. J. Ophth. **27**:589 (June); 693 (July); 820 (Aug.) 1944.

rates being over + 20 per cent and up to 85 per cent. In the other 5 patients it resembled more the dissociated type of opthalmopathy,[3] with low metabolic rates.

In 7 patients the condition was considered toxic enough to require reduction of their basal metabolic rates with thiouracil or propyl thiouracil. For these patients exophthalmometer readings were made for an average of 5.7 months. Six of the 7 were followed for three months or more. In this group there was a significant average increase in the exophthalmos of 1.8 mm. in the right eye; in 5 it was 1.5 mm. or over. The average increase in the left eye was 1.7 mm., 3 showing a progression of 2.0 mm. or more. In only 3 was there subjective or objective improvement in orbital pain, edema or corneal ulceration.

Four patients with mild toxicity which permitted treatment with Lugol's solution alone were given desiccated thyroid in addition for relief of the exophthalmos. In these patients the average basal metabolic rate increased 13 per cent as compared with a decrease of 24 per cent in the preceding group. It should be emphasized that the group of patients with malignant exophthalmos who were treated with thiouracil or propyl thiouracil alone were much more toxic than the group who received Lugol's solution and desiccated thyroid. For the latter patients exophthalmometer readings were made for an average period of thirteen and a half months, 3 being followed for over eight months. In these patients a significant average decrease of 1.1 mm. for each eye was noted instead of an average increase of exophthalmos. Two of the 4 showed some objective or subjective relief of edema and other evidences of improvement.

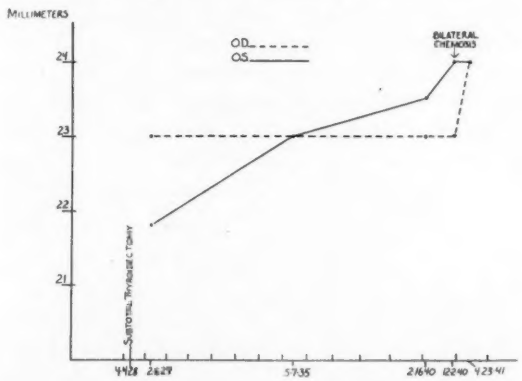
## COMMENT

The results in 28 patients with thyrotoxicosis without malignant exophthalmos who were treated with thiourea derivatives differ from those which Dobyns [1c] found in a similar group of 11 patients. Seven of his 11 patients showed an increase of 1.5 mm. or more. He included a few patients, however, who apparently had malignant exophthalmos, 1 showing a progression of 4.75 mm. His observations in 233 patients after thyroidectomy [1b] indicated an increase in prominence of the eyes in all but 9, or 97 per cent. Two thirds of the patients showed a significant increase of over 1 mm. Soley [1a] found that 50 per cent of patients with exophthalmic goiter showed a significant increase in exophthalmos of 1.5 mm. or more in an average of ten months after thyroidectomy. Twenty-five per cent showed an increase of 0.5 to 1.0 mm. The results with thiouracil were better than either of these surgical results, an increase of over 1 mm. occurring in the right eye in 1 and in the left eye in 2 (a total of 10 per cent). These findings, as might be expected with a slower method of treatment of thyrotoxicosis, are

in accord with those reported by Soley [1a] after roentgen therapy. In his group only 20 per cent showed a significant increase.

It is possible that the separation of patients with "malignant" exophthalmos from those with nonmalignant exophthalmos in the evaluating of the statistics has resulted in some of the difference between the results reported here and those of Dobyns. I think, however, that this distinction is an important one since, as a rule, patients with malignant exophthalmos in whom the metabolic rates are high show an increase in exophthalmos regardless of the type of treatment used for the thyrotoxicosis.

An evaluation of the final position of the eyes in these patients will require many years of observation, as illustrated by the patient whose course is shown graphically in the accompanying chart.




Progressive exophthalmos in a patient followed for eleven years.

He experienced progressive exophthalmos for at least eleven years after a subtotal thyroidectomy had been performed. When he was last seen, typical malignant exophthalmos had developed.

## SUMMARY

1. Twenty-eight patients with thyrotoxicosis and without malignant exophthalmos treated with thiourea derivatives alone had no significant average increase in exophthalmos when subjected to weekly exophthalmometer readings for an average period of four months.

2. Ten per cent of the patients showed a significant increase in exophthalmos, as compared with an incidence of 50 to 66 per cent reported by other authors after thyroidectomy and with an incidence of 20 per cent reported after roentgen therapy for thyrotoxicosis.

3. Seven patients with high basal metabolic rates and some evidence of malignant exophthalmos treated with thiourea derivatives alone

experienced a significant average increase in exophthalmos of 1.8 mm. over a period of observation of 5.7 months.

4. Four patients with low metabolic rates and malignant exophthalmos treated with Lugol's solution and desiccated thyroid showed no increase in exophthalmos over a period of 13.5 months.

5. It is important to distinguish between patients with malignant exophthalmos and those without it when evaluating changes in the eyes resulting from medical therapy for thyrotoxicosis.

# LOBAR ADENOCARCINOMA OF THE LUNG SIMULATING PNEUMONIA

## Report of Two Cases

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JAMAICA, N. Y.

RECENTLY, within a period of a few months, autopsy was performed in 2 cases at the Queens General Hospital, in both of which the true nature of an extensive pneumonic consolidation was not clearly recognized until microscopic study revealed diffuse adenocarcinoma. In neither of the cases could a primary adenocarcinoma be seen outside the lungs, nor could an exact origin from a bronchus be demonstrated. Though the condition is included in all anatomic classifications of pulmonary tumors, such cases are distinctly infrequent.

### REPORT OF CASES

CASE 1.—A 31 year old white housewife was admitted to the Queens General Hospital, complaining of shortness of breath and cough. Six months before admission, cough with scant expectoration developed. Two months later, the patient had pain in the right side of the chest, which was called pleurisy. One month after that, she visited the Department of Health Chest Clinic. A roentgenogram showed nodular fibrosis of the entire right side of the chest, with a thickened pleura, and increased pulmonic markings in the left lung (fig. 1). Reexamination one month later showed a similar picture on the right side and beginning nodular infiltration in the left pulmonary field. Examinations of concentrated sputum for acid-fast bacilli had negative results. In the two weeks before admission to the hospital, the cough and dyspnea grew severe. She was critically ill when admitted. The temperature was 101 F. The white blood cell count was 18,700, with 92 per cent polymorphonuclear leukocytes. A roentgenogram showed a diffuse dense homogeneous shadow throughout the entire right side of the thorax and a nodular type of parenchymal infiltration in the left lung (fig. 2). The previous roentgenograms of the chest were not available, and the clinical impression was that of tuberculous pneumonia of the right lung with spread to the left side. The patient died forty-eight hours after admission.

Autopsy revealed a completely solidified right lung, which, on macroscopic examination of sections, presented a dry grayish white surface with a pale yellow cast. This gross appearance suggested typical caseous tuberculous pneumonia. Throughout the left lung there was a nodular infiltration, the nodules being pale,

Read before the New York Pathological Society, Feb. 28, 1946.

From the Department of Pathology, Queens General and Triboro Hospitals, Jamaica, Long Island, New York.

grayish white and 0.5 to 1 cm. in size (fig. 3). The pleural surfaces were studded with similar nodules. The mediastinal lymph nodes were not enlarged. The left adrenal gland was partly replaced by a firm white mass. The right kidney presented small white nodules, 0.5 to 1 cm. in size. Though the nodules in the kidney and the adrenal gland suggested metastatic tumor, no primary focus could be seen outside the lung in such sites as the thyroid gland, breast or ovaries. No one particular bronchus could be incriminated as a point of origin.

Microscopic examination of sections from the right lung revealed diffuse adenocarcinoma. The alveolar walls formed a supporting network for the tumor. The alveoli were lined by columnar tumor cells. These cells were, in many places,

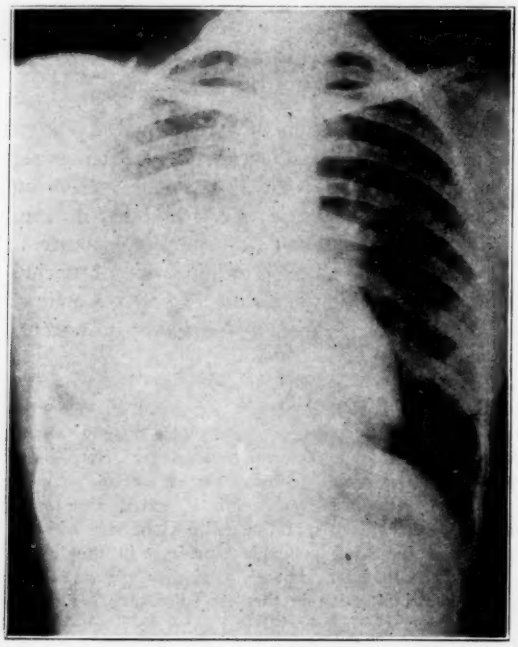

Fig. 1 (case 1).—Roentgenogram of the chest, three months after onset of cough. Nodular fibrosis of the right lung and increased pulmonic markings in the left pulmonary field are shown.

multilayered and grew in papilliferous folds projecting into the lumen. Within the alveoli lined by tumor cells, there were groups of free tumor cells, histiocytes, polymorphonuclear leukocytes and cellular debris. This alveolar content probably produced the yellow hue noted in the gross specimen on the cut surface. Not only the alveoli, but most of the bronchioles, were lined by tumor cells. The cells did not secrete mucus and were not ciliated. They exhibited considerable irregularity and presented many mitotic figures. There was no increase in elastica tissue in the alveolar walls. Tumor cells could be seen growing through the pulmonic alveolar vents. They were present in the peribronchial and perivascular lymphatic vessels and in the lymphatic vessels of the interlobular septums (figs. 4 and 5).

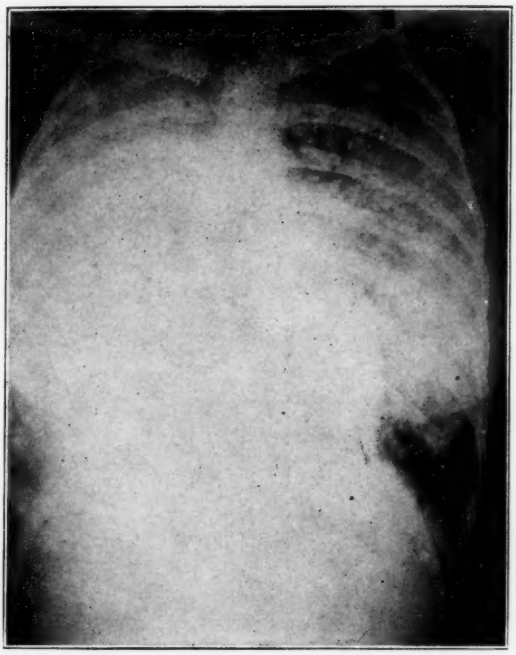

Fig. 2 (case 1).—Roentgenogram of the chest taken forty-eight hours before death, showing a diffuse homogeneous shadow throughout the right side of the thorax and a nodular infiltration in the left lung.

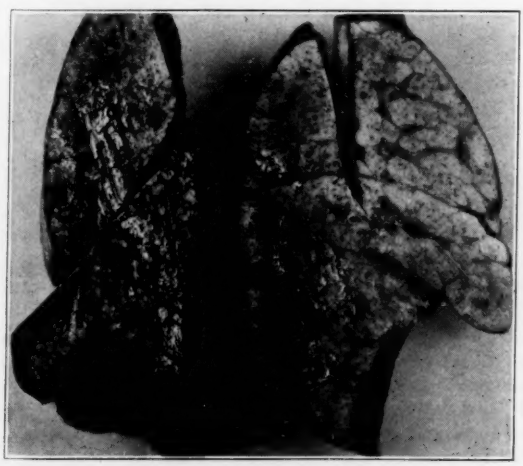

Fig. 3 (case 1).—Completely solidified right lung, with nodular infiltration throughout the left lung.

Sections through the left lung showed tumor cells within lymphatic vessels. The tumor nodules dispersed throughout the parenchyma were obviously metastatic. The presence of metastatic adenocarcinoma in the hilar lymph nodes, adrenal gland and kidney was verified in microscopic examination of the sections. An incidental observation was adenomyosis of the uterus.

The case was considered to be one of diffuse adenocarcinoma of the right lung, with metastases to the left lung, hilar lymph nodes, adrenal gland and kidney.

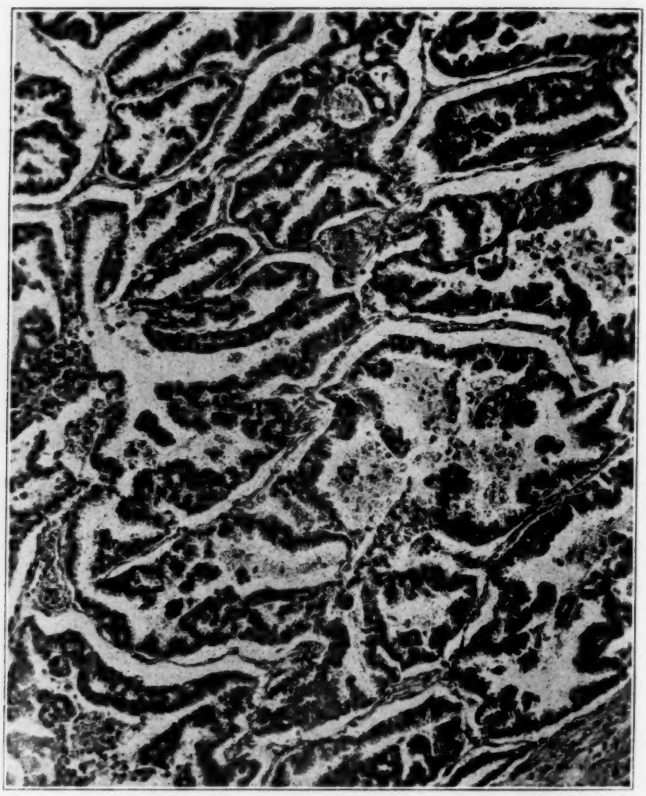

Fig. 4 (case 1).—Photomicrograph of tissue from the right lung, showing diffuse adenocarcinoma, with the tumor cells lining the alveolar walls.

CASE 2.—A 73 year old white woman was admitted to the Queens General Hospital, with a two months' history of cough and blood-tinged sputum. A roentgenogram, taken six days before admission, showed increased density over the lower half of the right lung, another area of increased density and radiating shadows in the upper lobe of the right lung and prominent bilateral hilar shadows. A diagnosis of tuberculosis was entertained. No positive reaction for tubercle bacilli was obtained in tests of the sputum throughout the subsequent five months' course. Thin straw-colored fluid accumulated in the right side of the chest, which

required repeated tapping. A roentgenogram, taken two weeks after admission, showed a nodular infiltration involving almost the entire right lung and radiating shadows in the upper lobe of the right lung, as previously noted, and prominent bilateral hilar shadows. There was, also, fluid at the base of the right lung, with a pneumothorax space inadvertently produced by a thoracic tap (fig. 6). Another roentgenogram, taken three weeks before death, showed clouding of the right pulmonary field, due to fluid, and accentuated pulmonary markings in the

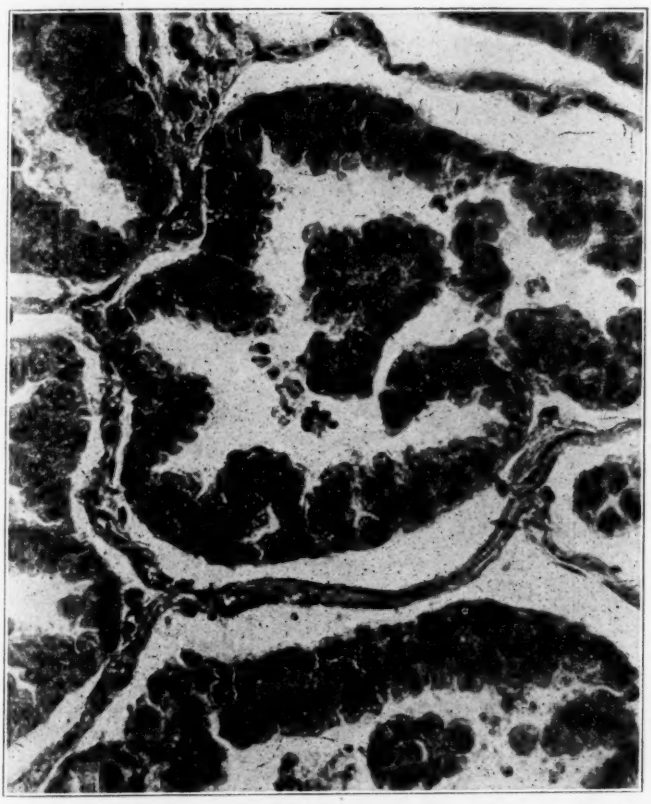

Fig. 5 (case 1).—Photomicrograph of tissue from the right lung. High power magnification of figure 4.

left side of the chest. A bronchoscopic examination was not made, because of the patient's poor condition. Death occurred five months after admission and seven months after the onset of symptoms. The diagnosis now favored was bronchiogenic carcinoma, though tuberculosis could not be excluded.

Autopsy revealed about 2 liters of sanguineous fluid in each pleural cavity. Macroscopic examination of sections revealed the right lung to be completely consolidated, the cut surface firm, gray and so mucoid that a gross diagnosis of lobar pneumonia caused by Klebsiella pneumoniae was made (fig. 7). Within

the lower lobe of the right lung, one old calcified tuberculous focus was recognized. The left lung was studded with small nodules of firm gray tissue. A lymph node in the right hilar region appeared infiltrated. There were small round nodules, averaging 0.5 cm., in both adrenal glands. As in the previous case, no primary focus could be seen outside the lungs, nor could any one particular bronchus in the lung be incriminated as a point of origin.

Microscopic examination of sections from the right lung revealed alveoli lined by mucus-secreting tumor cells. In addition to their mucus-secreting character, the tumor cells were tall, columnar, and nonciliated. They lined the alveoli in single layer, or the lining was multilayered. This lining was frequently thrown

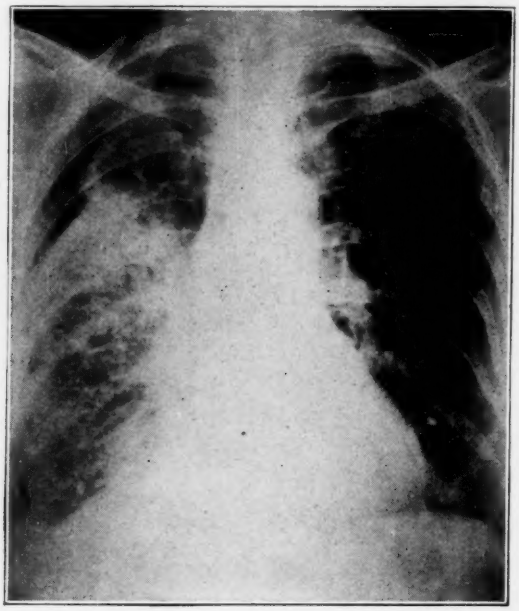

Fig. 6 (case 2).—Roentgenogram of the chest taken about five months before death, showing nodular infiltration in the right lung and fluid at the base.

into papillary folds projecting into the acinar lumen, at times completely filling it (fig. 8). In many areas the tumor cells lost their columnar outline and were irregular and polyhedral, with large bizarre nuclei. Bronchioles retained their normal lining, though groups of tumor cells could be seen in the lumen. Fibrotic thickening of the alveolar walls was noted, as well as thickening of the interlobular septums and pleura. There was considerable deposition of anthracotic pigment. Tumor cells were seen in the lymphatic vessels.

In the left lung, tumor extension along peribronchial and perivascular lymphatic vessels was noted. Even in the lymphatic vessels, the tumor cells showed a tendency to line the lymphatic walls. Sections of lung also showed some traces of old tuberculosis. Microscopy confirmed the presence of metastatic mucogenic adenocarcinoma in the adrenal glands and revealed metastatic tumor in the liver.

The case was considered to be one of diffuse mucogenic adenocarcinoma of the right lung, with metastases to the left lung, hilar lymph nodes, adrenal glands and liver.

COMMENT

To clinicians, the cases presented herein offer a distinct problem in diagnosis. The disease is frequently thought to be some form of pneumonia. Careful consideration should include in the differential diagnosis the possibility of tumor infiltration in the lungs. To pathologists, the differentiation of these lesions from pneumonic consolidation offers considerable difficulty on gross inspection.

Fig. 7 (case 2).—Right lung, showing consolidation.

Such cases, also, present several points of interest:

1. Are they cases of primary adenocarcinoma of the lung or has a primary growth at some other site been overlooked?

A review of 4,500 consecutive autopsies at Queens General Hospital revealed 79 cases of metastatic adenocarcinoma to the lung, with the primary focus elsewhere in the body. Three of these cases presented what could be called massive consolidation of a lung by tumor. Two of the 3 were extremely interesting, because the only possible primary growth in each was a miniature carcinoma of the prostate gland. In the

third case the primary growth was in the breast. Histologically, the tumors grew at times diffusely and at times lining the alveolar walls.

Among the 4,500 cases, 26 instances of primary adenocarcinoma of the lung were noted, with the primary focus in a bronchus. None of these presented complete consolidation of a lung or lobe. Only the 2 cases described in this report presented lobar solidification, without a distinct point of origin.

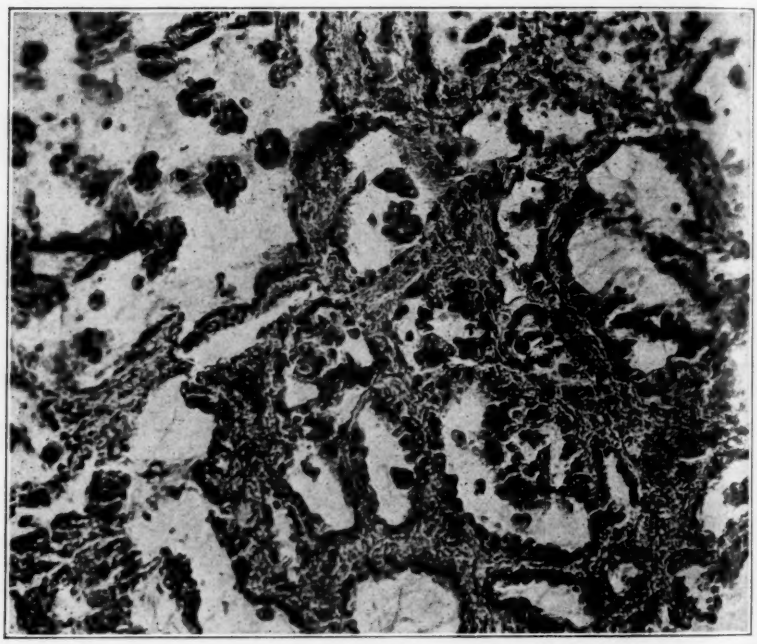

Fig. 8 (case 2).—Photomicrograph of tissue from the right lung, showing diffuse mucogenic adenocarcinoma, with the tumor cells lining the alveolar walls.

One could state simply that both metastatic adenocarcinoma and primary adenocarcinoma can, on rare occasion, consolidate a lung.

The growth pattern of the tumor, that of carcinoma cells lining the alveoli, does not help resolve the problem, since this is often seen in any adenocarcinoma in the lung, whether primary or metastatic.

Finally, reports of cases in the literature, reviewed by Neuberger and Geever,[1] support the contention that diffuse adenocarcinoma can occur in the lung without a demonstrable primary focus elsewhere.

1. Neuberger, K. T., and Geever, E. F.: Alveolar Cell Tumor of the Human Lung, Arch. Path. **33**:551 (April) 1942.

2. If the primary site is in the lung, where is the point of origin of these tumors? Do they arise in the bronchial tree, or can they be called alveolar cell carcinomas?

Of the abundant literature on the subject, it will suffice for this presentation to point out: (*a*) The existence of an epithelial lining to the alveolar wall is still disputed, and, in general, negated by most authors. (*b*) A diagnosis of alveolar cell carcinoma can be made only if there is evidence of independence of the bronchial system.

Independence of the bronchial system cannot be established when there is extensive pulmonary involvement. Satisfactory proof can be obtained only from careful sectioning of a small tumor observed incidentally at autopsy or lobectomy. If evidence of independence of the bronchial system cannot be demonstrated, it follows that absolute proof of origin in the alveolar wall cannot be established.

3. May a theoretic origin for this tumor process exist in the well known instances of alveolar epithelization in human beings?

Bell,[2] and Geever, Neuberger and Davis[3] pointed out the many circumstances in which there occur thickening of alveolar walls, loss of function and lining of alveoli with a low cuboid cell. Whether this cell arises from the terminal bronchiole or the alveolar wall is still disputed.[4] The proliferation is a response to a chronic irritant. The type of proliferation may be said to be analogous to the polypoid growth of the intestinal mucosa during the healing of ulcerative colitis. The proliferating cell is clearly benign in appearance. No proof exists today to support the suggestion that these alveolar lining cells may be precancerous.[5]

4. Could these tumors have multiple simultaneous points of origin?

The attempt to establish a multicentric origin for malignant tumors is always difficult. Metastases by way of lymphatic vessels, blood vessels and even direct implantation can occur rapidly and extensively. Certainly, in the 2 cases presented here, there is abundant evidence of lymphatic extension and, therefore, no justification for the assumption of a multicentric origin.

The possibility of simultaneous multiple points of origin from an alveolar lining, diffusely condemned by the action of some virus, bac-

2. Bell, E. T.: Hyperplasia of Pulmonary Alveolar Epithelium in Disease, Am. J. Path. **19**:901, 1943.

3. Geever, E. F.; Neuberger, K. T., and Davis, C. L.: The Pulmonary Alveolar Lining Under Various Pathologic Conditions in Man and Animals, Am. J. Path. **19**:913, 1943.

4. Herbut, P. A.: Bronchiolar Origin of "Alveolar Cell Tumor" of the Lung, Am. J. Path. **20**:911, 1944.

5. Ikeda, K.: Alveolar Cell Carcinoma of the Lung, Am. J. Clin. Path. **15**:50, 1945.

terial agent or chemical, physical or other stimulant, raises the next question.

5. What, if any, is the relationship among diffuse or nodular adenocarcinoma of the lung, pulmonary adenomatosis in human beings, induced or spontaneous pulmonary tumors in mice and jagziekte infection in sheep?

Jagziekte in sheep,[6] probably a virus infection, presents a consolidated lung due to the lining of alveoli by a cuboid or columnar cell. At times this epithelium may proliferate in papilliferous fashion. The cells are benign in appearance and show no tendency to metastasize. However, there has been 1 case reported in the literature, by Aynaud,[7] in which metastases were said to have occurred.

Induced pulmonary tumors in mice have been shown to arise in multicentric fashion and to be independent of bronchioles (Grady and Stewart [8]). The nodules present groups of alveoli lined by cuboid or columnar cells. The cells usually have a benign appearance. Metastases seem to be infrequent. Wells, Slye and Holmes,[9] in discussing spontaneous tumors in mice, pointed out that they can, on rare occasion, metastasize. These authors stated that "it is extremely difficult to distinguish between benign and malignant tumors in mice, since some with a benign appearance may metastasize and others with a wilder growth, may remain localized."

Reports of cases of pulmonary adenomatosis in human beings have appeared in the literature [10] and have aroused considerable discussion in

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6. Cowdry, E. V., and Marsh, H.: Comparative Pathology of South African Joogziekte and Montana Chronic Progressive Pneumonia of Sheep, J. Exper. Med. **45**:571, 1927. Dungal, N.: Epizootic Adenomatosis of Lungs of Sheep: Its Relation to Verminous Pneumonia and Joogsiekte, Proc. Roy. Soc. Med. **31**:497, 1938.

7. Aynaud, M.: Origine vermineuse du cancer pulmonaire de la brebis, Compt. rend. Soc. de biol. **95**:1540, 1926.

8. Grady, H. G., and Stewart, H. L.: Histogenesis of Induced Pulmonary Tumors in Strain A Mice, Am. J. Path. **16**:417, 1940.

9. Wells, H. G.; Slye, M., and Holmes, H. F.: The Occurrence and Pathology of Spontaneous Carcinoma of the Lung in Mice, Cancer Research **1**:259, 1941.

10. (*a*) Bell.[2] (*b*) Helly, K.: Ein seltener primärer Lungentumor, Ztschr. f. Heilk. **28**:105, 1907. (*c*) Oberndorfer, S.: Zellmutationen und multiple Geschwulstenstehungen in den Lungen, Virchows Arch. f. path. Anat. **275**:728, 1930. (*d*) Bonne, C.: Morphological Resemblance of Pulmonary Adenomatosis (Joogsiekte) in Sheep and Certain Cases of Cancer of the Lung in Man, Am. J. Cancer **35**:491, 1939. (*e*) Richardson, G. O.: Adenomatosis of the Human Lung, J. Path. & Bact. **51**:297, 1940. (*f*) Sims, J. L.: Multiple Bilateral Pulmonary Adenomatosis in Man, Arch. Int. Med. **71**:403 (Dec.) 1943. (*g*) Taft, E. B., and Nickerson, D. A.: Pulmonary Mucous Epithelial Hyperplasia (Pulmonary Adenomatosis): Report of Two Cases, Am. J. Path. **20**:395, 1944. (*h*) Wood, D., and Pierson, P.: Pulmonary Alveolar Adenomatosis in Man: Is This Same Disease as Joogsiekte in Sheep? Am. Rev. Tuberc. **51**:205, 1945.

recent years. The disease has been described as diffuse or nodular, but more frequently the latter. The cells lining the alveoli have been shown to be tall cuboid or columnar, at times growing in papilliferous fashion. Though the cells were considered benign in appearance, Wood and Pierson[10h] pointed out that in their case the cells showed active hyperplasia. Sims [10f] described his case as presenting, in areas, anaplasia, and Bonne [10d] stated that the lining cells in his case were dark and irregular, with mitoses. None of these cases presented metastases. Dacie and Hoyle[11] presented 1 case of the disease which they called malignant adenomatosis and which, they claimed, showed a fine gradation histologically from benign adenomatosis to definite invasive carcinoma. Another group of cases has been described in the recent literature, in which the authors pointed out a pattern of growth similar to pulmonary adenomatosis, but with more irregular cell structure and metastases.[12]

In all three groups of pulmonary adenomatosis, occurring in human beings, in mice and in sheep, the process seems to be benign epithelial hyperplasia, with possible malignant changes. An analogy may be drawn between these instances of pulmonary adenomatosis and multiple adenomatous polypi seen in the colon; they are benign though potentially malignant.

Though too little is known today to permit any clearcut conclusion, one can postulate that one or more nodules in pulmonary adenomatosis can be the precursor of a carcinoma. The observation of diffuse or nodular adenocarcinoma in the lung does not, of necessity, imply preexisting adenomatosis.

## SUMMARY AND CONCLUSIONS

Two cases of diffuse adenocarcinoma of the lung, with metastases, are presented.

The evidence would indicate the following conclusions:

1. The growths are primary in the lung, but metastases from a latent primary glandular focus outside the lung should be carefully excluded.

2. They arise from the mucosa of the bronchial tree beyond the larger bronchi, the point of origin being obscured by the extensive growth involvement.

3. A source of origin from preexisting epithelized alveoli cannot be proved.

4. A multicentric origin cannot be established.

11. Dacie, J. V., and Hoyle, C.: Malignant Adenomatosis (Alveolar Cell Tumor) of the Lungs, Brit. J. Tuberc. **36**:158, 1942.

12. Herbut.[4] Ikeda.[5] Sweany, H. C.: A So-Called Alveolar Cell Cancer of the Lung, Arch. Path. **19**:203 (Feb.) 1935. Neuberger, K. T.: Primary Multiple Alveolar Cell Tumor of the Human Lung: Report of Case, J. Thoracic Surg. **10**:557, 1941.

5. To date, there is no proved relationship between diffuse adenocarcinoma of the lung and pulmonary adenomatosis.

Note—Since the manuscript was submitted, 2 additional cases have been encountered. In 1 a gross diagnosis of Friedländer's bacillus pneumonia was made at the time of the autopsy on the basis of the gross appearance. This seemed to be confirmed by the isolation of this organism on smear and culture. Subsequent histologic sections presented diffuse adenocarcinoma identical in every detail with the disease in the second case.

# Progress in Internal Medicine

## REVIEW OF NEUROPSYCHIATRY FOR 1947

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THIS year marks the passing of Pierre Janet. He died at the age of 87, having courageously passed through war and through family bereavement in the last few years. In 1906 he was invited to come to America to give a series of lectures at the opening of the new buildings of the Harvard Medical School. These lectures became his famous book, "The Major Symptoms of Hysteria." [1] In 1936 he came back to Harvard's tercentenary and delivered a lecture, as full of sparkle and ideas as he was thirty years before. His work bridged the gap between centuries; with Freud and Meyer he brought psychologic medicine from its descriptive and classifying stage into its present dynamic state. His descriptions of psychic states were remarkable, but he was more interested in processes and in psychic developments. He did not believe in the arbitrary and artificial separation of neuroses from psychoses, considering it entirely false from the clinical standpoint. In his early years he was much interested in hypnosis. His last extensive work was a book on psychotherapy published in 1920. Few men have been as brilliant and enlightened on a subject for so many years.

A number of interesting books have appeared recently. Gordon Holmes,[2] the man who might be looked on as the dean of living neurologists, has written a little book giving his views on neurology and especially on methods of examination. "The Neurology of the Ocular Muscles" by David G. Cogan [3] is a two hundred page book of unusual merit. The author's wide clinical experience and skill in laboratory technic make the exposition of anatomy, physiology and symptomatology especially good. His concept of "tonus" as the "sum-total effect of the various neurochemical processes affecting the length of a muscle and, consequently, the position of an organ" is unusual but pleasing to the reviewer. It disposes of this vague term "tonus" by proclaiming

1. Janet, P.: The Major Symptoms of Hysteria: Fifteen Lectures Given in the Medical School of Harvard University, New York, The Macmillan Company, 1907.

2. Holmes, G.: Introduction to Clinical Neurology, Baltimore, Williams & Wilkins Company, 1946.

3. Cogan, D. G.: Neurology of the Ocular Muscles, Springfield, Ill., Charles C Thomas, Publisher, 1948.

its identity with all muscular contraction. In fact Cogan goes on to say: "Movements of the eyes are brought about by increase in tone of one set of muscles or relaxation in tone of the antagonistic muscles, or as is usually the case by both." He discusses the labyrinthine control of the extraocular muscles, speaking of "maintained postural deviations" controlled by the otoliths and "postural movements" controlled by the semicircular canals. This is better terminology and is more physiologically understandable than "tone," especially because the author believes that the ocular muscles have no proprioceptive endings or nerves. Knowledge of the position of the eyeballs depends on vision. The facts arrayed to back up this opinion are convincing. The text is arranged according to physiology and signs. Disease entities are not emphasized. The book is well illustrated by sixty-nine diagrams and photographs.

Another notable book is "Brain and Intelligence" by W. C. Halstead,[4] of the University of Chicago. His aim is "to set up an operationally defined conception of biological intelligence in terms of number and kind of factors involved." Thirty control subjects and 207 persons with injured brains were examined by means of a battery of tests. The results were correlated, and the intercorrelations were treated by factor analysis. This yielded four factors interpreted as "C," a central integrative field factor, "A," a basic ability for abstraction, "P," an undistorted "power" factor of the functioning brain closely related to affect and "D," a directional factor for the exteriorization of intelligence. These gave a quantitative basis for estimating intelligence which the author then applied to patients. He worked out an "index of impairment" for patients who had undergone lobectomies, lobotomies and head injury. He concludes that the frontal lobes are "the areas most essential to biological intelligence." No short review can do more than indicate that here is an important piece of work pointing the way to new and better methodology in a field too much influenced by unreliable clinical impressions.

Leon Saul[5] in his "Emotional Maturity" has undertaken one of the most difficult of tasks. He has endeavored to present a description of the mind as a rough equivalent of the gross anatomy and physiology of the body. His training in neurophysiology, psychiatry and psychoanalysis has fitted him well for the task. He respects the scientific method and defines terms. "Mind" is to him "the activity of the highest level of the brain, which we perceive and experience as our thoughts

4. Halstead, W. C.: Brain and Intelligence: A Quantitative Study of the Frontal Lobes, Chicago, University of Chicago Press, 1947.

5. Saul, L. J.: Emotional Maturity: The Development and Dynamics of Personality, Philadelphia, J. B. Lippincott Company, 1947.

and feelings and express in psychologic terms." Man is an organism, reacting and striving. The psychodynamic study of this biologic activity is the field of the psychiatrist who would understand personality. Psychodynamics is the study of how the mind works or a study of the forces which motivate us.

It has long been the custom among psychiatrists to explain abnormal behavior on the vague basis of "emotional immaturity." Saul pins this down in his first chapter, saying:

> We have now mentioned eight of the major aspects of the emotional development of man and some of the characteristics of maturity to which each leads. This list is not exhaustive; these aspects are interrelated and are not all on the same level. But we have tried to discern some of the forces in the personality which are basic and from which the many other attributes of maturity are derived. We have seen that when the development is fulfilled the adult is *predominantly* independent and responsible, with little need to regress, and also is giving and productive, although still able to relax and to receive normally; he is cooperative rather than egotistical and competitive; he is in relative harmony with his conscience, which easily integrates with his mature feelings and behavior; his sexuality is free and integrated with mating and responsible productive activity, both sexual and social; his hostility towards others and toward himself is minimal but is freely available for defense and constructive use; his grasp of reality is clear and unimpaired by the emotional astigmatisms of childhood; and freed from childhood patterns, he is discriminating and highly adaptable. And among the many results of such development, his anxiety is at a minium.

These cardinal points are taken up extensively in eight separate chapters.

"Man's suffering on this earth is caused predominately by man himself and is a manifestation of his emotional immaturity." This epigrammatic sentence from page 12 seems to express the main theme of the book. It is not far from being the key to the neuroses which is expressed on page 316 as "the tendency in everyone to regress under stress to earlier childhood ways of thinking and reacting." Neurosis is defined as "a failure of adaptation and a disturbance of the patient's emotional development." The essence of neurosis is said to be (page 291) "the undue predominance of untoward childhood reactions." Saul wisely emphasizes that although he is writing about the psychic determinants of neurosis there are others of great importance, such as heredity, physical constitution and fetal development.

The book is readable, forceful and informative. While it attempts a synthesis that is impossible in 1948, it makes a step forward in clarifying the concept of the neuroses. There is a lighter touch in certain phrases and illustrations that is welcome. Some of the diagrams are helpful, while others are rather overwhelming. The "first approximation" of expressing neurosis in a mathematical formula shows that the author has reached maturity and does not fear criticism!

SEXUAL BEHAVIOR

Kinsey, Pomeroy and Martin,[6] three nonmedical scientists from the University of Indiana, have given to medicine and especially to psychiatry some much needed facts. When a physician was asked about sexual habits, normal and abnormal, he usually had little to fall back on except somewhat impressionistic clinical experience. Medical literature did not give the answers he needed. Now this book on "sexual behavior in the human male" supplies the data needed. It is based on interviews with 5,300 white men, representing six hundred and ninety-eight samples of different population. The senior author is a professor of zoology, and the approach is taxonomic, implying that the author's interest is merely to name, describe and classify. Mostly they stick to their last and do a remarkably good job. Occasionally they make challenging statements. For example, in discussing the so-called perversions, they say: "It may well be questioned how far an individual is responsible for his behavior when he conforms to the pattern of his social level, even though he may thereby be involved in a transgression of the law" (page 681).

Some of the clinical problems that face the physician are described (on page 578) as follows:

> A list of the social problems which most often arise out of human sexual activity would give first places to venereal disease, bastardy, rape, and the contribution by adults to the delinquency of minor children. On the other hand personal conflicts most often develop over masturbation, oral contacts and the homosexual. These are the three that need especial help—not because they are rare, but because they are widespread, and because nearly every male in the population is at one time or another involved in one or more of them. These are the three that are most often encountered by the clinician, not because men are frequently abnormal or recently become perverse, but because all three of these are part of the basic biologic pattern of mammalian sexual behavior, and because no legislation or social taboos have been able to eliminate them from the history of the human animal.

The point for the physician to remember is that oral-genital stimulation is not rare and is not "unnatural." It occurs in most mammals, and it occurs, according to Kinsey, in 60 per cent of the case histories of the more educated people, in 20 per cent of those persons of the high school level of education and in 11 per cent of those of the poorly educated. These last are the ones who have most taboos and look on the sex habits of the educated as "perverse" and "unnatural." They also taboo nakedness in intercourse, which can hardly be called "unnatural." Doubtless because of the strong taboo, there is much concealment in their histories on this point, and the

6. Kinsey, A. C.; Pomeroy, W. B., and Martin, C. E.: Sexual Behaviour in the Human Male, Philadelphia, W. B. Saunders Company, 1948.

figures should be raised. The subject is important because many divorces are caused by this "perverted" sexual behavior. Considering the behavior medically, it would seem more scientific not to say that the act in itself is abnormal or unnatural but to lay stress on the individual situation and on the selfishness or "cruelty" of the spouse who insists on such acts in spite of the disturbing effect on his partner.

The book has been so widely reviewed in the general press that I will not transcribe much of the material. It is given abundantly in tables and should be read in the context and with an understanding of the statistical procedures to be of full value. A few of the more important data may be summarized as follows:

The frequency of sexual outlet is indicated by the data on the number of orgasms per week of single white males. The average is highest for those between the ages of 15 and 20, a little over three times a week, and drops off gradually to 1.9 for those between 41 and 45. In the poorly educated group the average runs about a fifth higher than in the well educated group throughout the different ages. This may mean that conscientious scruples are more effective in the educated group or that satisfactions on a more intellectual plane take up some libido by sublimation. It might be explained in other ways. Kinsey has some data to show that devoutly religious males have much less extramarital intercourse (table 129).

In the poorly educated group between the ages of 15 and 35 masturbation averages about once a week and intercourse about twice a week. In the group with some college education this is reversed, intercourse averaging less than once a week and masturbation about twice. The highest rate of masturbation is found among those 15 years old in the educated group, the average for the number of times being 2.7 per week. The highest average rate of intercourse is found among the low education group aged 21 to 25, with an average of 2.3 per week.

The method of interviewing is given in chapter II. This is an admirable exposition of what an interview should be when the object is fact finding in connection with a frequently embarrassing subject. The success of these men seems to have been due to their extraordinary patience, great decency and human understanding. They seem to have been able to lead another man "into exposing his activities and his innermost thoughts." "Failing to win that much from the subject," it is stated, "no statistical accumulation, however large, can adequately portray what the human animal is doing." In other words, unless the interviewing is successful and brings out a good approximation of the truth, the whole project is useless. One is convinced that the authors have done a good job and that most of the data are valid and important.

A definition of "truth" in this situation is another matter. The authors are self-avowedly taxonomists and not psychiatrists or psycho-

analysts. Professional psychiatrists with training in psychoanalysis might bring up the question as to whether the reports of many of these persons actually were true, because in the sexual sphere repression may cause some very thorough forgetting and even false memories. Just this point is brought up emphatically by Kubie [7] in his trenchant review. The question cannot be answered until sample cases have been studied by psychiatric technic with a view to bringing out the repressed and subconscious material. To what degree such a study would modify the conclusions of the present book remains a matter of speculation. One might guess, however, that the main facts about overt sexual activity as here stated would stand up well, whereas the data concerning subjective responses, fantasies, childhood memories and homosexual activities might be modified considerably.

It is of importance to psychiatry to learn that in this taxonomic study the main postulates of psychoanalysis concerning infantile sexuality have been verified. Sexuality before the age of 8 seems to be diffuse and polymorphous. All sorts of varied stimuli set up sexual reactions. Orgasm in the male (except for ejaculation) has been observed at 5 months and frequently at 2 years. One 4 year old had twenty-six orgasms in twenty-four hours. As adolescence comes on, at 8 or 10 years, the stimuli causing erotic response become more concentrated in the genital organs. The concept of a "latency period" is not substantiated by Kinsey's observations.

There is no evidence that marked sexual activity in younger persons tends to make for less potency later. In fact, the evidence points to the opposite. The lower the cultural level the more premarital and extramarital intercourse is found. The lower group considers the upper "perverted" and the upper considers the lower "immoral"! About 85 per cent of all males have premarital intercourse. Between 30 and 45 per cent have extramarital relations. Some sort of homosexual experience is reported by 37 per cent of the total group. The incidence is 70 per cent in the lower education group at 16 years of age and 30 per cent in the higher education group. A great many of the homosexual contacts are incidental; the homosexual response is most often definite and repeated in preadolescence (6 to 10), through the "teens" and up to 25 years of age. Over 20 per cent of males between the ages of 6 and 26 are more than incidentally homosexual (fig. 170).

This brings up the question of what is "normal." If all homosexual activity is to be called abnormal, what can be done about it? Kinsey puts it this way:

> It means that at least 13% of the male population would have to be institutionalized and isolated, if all persons who were predominately homosexual

7. Kubie, L. K.: Sexual Behavior in the Human Male, by. A. C. Kinsey; W. B. Pomeroy and C. E. Martin, book review, Psychosom. Med., to be published.

were to be handled in that way. Since about 34% of the total population of the United States are adult males, this means that there are about six and a third million males in the country who need such isolation.

The statistical concept of "normal" in this case certainly is a challenge for physicians, penologists and sociologists. Not enough differentiation is made between the sexually active youth who is giving everything a rather thoughtless try and the older, compulsive homosexual. To the psychiatrist the numerical data suggest that what one is interested in particularly should be the individual case. By studying in each case what the endocrine and psychologic factors may be, the physician might decide who is "sick" and to what degree. Likewise the penologist can decide who is "good" and who is "bad." Both want to know how dangerous a given man is to the accepted habits of the community. Careful consideration should be given to what is meant by "normal," "good" or "well," as opposed to "abnormal," "bad" or "sick."

## CAUSES OF MENTAL DEFICIENCY

The older books on amentia lay emphasis on only two causes, inheritance and syphilis. For this reason the prevention and treatment of feebleminded ness have often been taken up with a pessimistic attitude by physicians. Educators have been more hopeful and have methodically gone ahead with what could be done for the individual ament. Gesell [8] broadens the concept a great deal, classifying developmental aberrations as (1) defective development, due to (*a*) aplasia, malformation and degenerative diseases or (*b*) lesions following trauma, infection, toxic agents, anoxia and irradiation, and (2) deviated development due to prematurity, endocrine disorder, sensory and motor handicaps, abnormal experience and personality defects.

The last two items bring in the great field of psychogenesis, which is discussed later under child psychiatry. The other categories have been made clearer by several recent investigations. In the endocrine field there is evidence that cretinism is associated with maternal hypothyroidism and that mongolism is related to maternal pituitary disorder.[9] More strictly in the field of genetics, Professor Muller, of the University of Indiana, has been recently awarded the Nobel Prize for showing that radiation may cause changes in the genes. This makes one think of various sorts of radiation as possible factors in causing mal-

8. Gesell, A. L., and Amatruda, C. S.: Developmental Diagnosis, ed. 2, New York, Paul B. Hoeber, Inc., 1947.

9. Benda, C. E.: Mongolism and Cretinism: A Study of the Clinical Manifestations, and the General Pathology of Pituitary and Thyroid Deficiency, New York, Grune & Stratton, Inc., 1946.

development of the nervous system. Incompatibilities in blood groups with respect to the Rh factor have been shown to be responsible for damage to the nervous system of newborn babies. The presence or absence of the Rh factor is apparently transmitted through the genes.[10]

Encephalitis of various sorts has been proved to be a cause of mental deficiency. Toxoplasmosis is one of the most recently recognized. Children having hydrocephalus, intracerebral calcification and chorioretinitis should be suspected, and they should be tested by serologic methods and by means of animal inoculation.[11] Rivers[12] lists fifteen viruses that may cause human encephalitis. Many of these affect children and may cause the various behavior disorders and mental defects with which pediatricians are familiar. Some of these diseases may be borne by mosquitoes[13]; both the equine encephalomyelitis and the "St. Louis type" of encephalitis have been isolated from Culex tarsalis. Equine encephalitis is commonest in children under 5 years of age. "Japanese B" encephalitis occurs in cows, horses, goats and fowl, and epidemiologic data suggest that the virus is carried by mosquitoes.[14] Although nothing is known of the organism responsible for Economo's disease, which used to be the common form of encephalitis, much new knowledge is coming to the clinician about other forms of encephalitis. A certain number of cases of mental defect are thus being explained.

Diseases of the mother causing injury to the fetus have been long known, but that rubella was one of these was brought to light only six years ago in Australia.[15] Gregg has shown that a long list of "congenital" defects can be laid to this cause, including deafness, microcephaly and mental retardation. A growing literature shows that this is an important source of amentia. Ingalls and Davies[16] believe that other

10. Levine, P.; Katzin, E. M., and Burnham, L.: Isoimmunization in Pregnancy: Its Possible Bearing on Etiology of Erythroblastosis Foetalis, J. A. M. A. **116**:825 (March 1) 1941.

11. Kabler, P., and Cooney, M.: Toxoplasmosis, Minnesota Med. **30**:637, 1947. Toxoplasmosis, editorial, New England J. Med. **237**:346, 1947.

12. Rivers, T. M.: Virus Diseases of the Nervous System, J. A. M. A. **132**: 427 (Oct. 26) 1946.

13. Meyer, K. F., and Eddie, B.: Knowledge of Human Virus Infections of Animal Origin, J. A. M. A. **133**:822 (March 22) 1947.

14. Sabin, A. B.: Epidemic Encephalitis in Military Personnel: Isolation of Japanese V Virus on Okinawa in 1945; Serologic Diagnosis, Clinical Manifestations, Epidemiologic Aspects and Use of Mouse Brain Vaccine, J. A. M. A. **133**:281 (Feb. 1) 1947.

15. Wesselhoeft, C.: Rubella, New England J. Med. **236**:978, 1947.

16. Ingalls, T. H., and Davies, J. A. V.: Mongolism Following Intercurrent Infectious Disease in Pregnancy, New England J. Med. **236**:437, 1947.

infections of pregnant women, such as influenza and mumps, may cause mongolism in the child if the infection occurs during the second month.

### CHILD PSYCHIATRY

The groundwork for child psychiatry was laid forty years ago by Binet, Freud, Eichorn and Healy. The important influence of Adolf Meyer is emphasized by Helen Witmer [17] in her introduction to "Psychiatric Interviews with Children"; she says that he was interested in the problem in the 1890's and gave child psychiatry a start in the early part of this century by his dynamic psychology. Healy directed the first child guidance unit, the Juvenile Psychopathic Institute in Chicago, which opened in 1909. His career since then until his recent retirement has been one of leadership in a rapidly expanding field. Describing the recent changes in attitude and practice, Witmer says (page 12):

> By the end of the mid-nineteen-thirties, however, a change in child guidance psychiatry was in process. The stimulating conceptions derived from psychoanalytic work with young children were beginning to influence practice. Play was found to be an adequate substitute for discussion as a means of revealing young children's difficulties and giving help in overcoming them. Psychiatric interviews themselves became less intellectual, as the implications of the dynamic theory, for therapy as well as for etiology, became apparent. Less emphasis was put on symptoms, as expressed in behavior and personality traits, and more on feelings and desires. In short, psychiatric study and prescription gave way to psychiatric treatment.

The therapists took off their good clothes and their adult veneer and got down on the nursery floor with the children to see what they were up to. By doing this they learned the language of the child, verbal and nonverbal, and made a relationship which they used not only for diagnosis but for therapeutic ends. The extraordinary patience of the therapists as well as their feeling for the child and their insight into his disordered personal relations frequently bring about remarkable improvement in behavior. The case histories recounted in Witmer's book and in the first two volumes of "The Psychoanalytic Study of the Child" [18] give good evidence of this.

The technic of child analysis is different from that of adult psychoanalysis. The child cannot be expected to talk about his problems. Mahler [19] says:

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17. Witmer, H. L.: Psychiatric Interviews with Children, New York, The Commonwealth Fund, 1946.

18. Freud, A.; Hartmann, H., and Kris, E.: The Psychoanalytic Study of the Child: An Annual, New York, International Universities Press, Inc., 1945, vol. 1; 1946, vol. 2.

19. Mahler, M. S.: Child Analysis, in Lewis, N. D. C., and Pacella, B. L.: Modern Trends in Child Psychiatry, New York, International Universities Press, 1945.

We have plenty of valuable substitutes for it in the use, as analytic material, of all productions and functions of the child: play, drawing, dramatic acting, competitive games, gymnastic stunts, handy craft, story telling, continual day dreams, fantasies, and the like, are all our tools. We leave the initiative entirely to the child and, though we participate, we try to get the lead from the patient in order that we may avoid introducing elements into the situation not pertinent to the child.

The application of psychoanalysis to childhood problems had beginnings as far back as 1909, when Freud analyzed the phobia of a 5 year old boy. Psychoanalysts from the beginning dealt with childhood memories in their adult patients, and these memories pointed to the great importance of early childhood in the development of future patterns of behavior. No direct attack on the problem was made until Anna Freud, a schoolteacher, took psychoanalysis into the educational field. She published "An Introduction to the Technique of Child Analysis" in 1928,[20] and in 1932 started the "Zeitschrift für Psychoanalytische Paedagogik." These beginnings were interrupted in 1938 by the Nazis. Freud and his daughter moved to London, where he died in 1939. She went on with her work among children and made a great contribution both to the war and to psychology by studying the displaced children and describing their reactions to separation from parents, foster care, bombing and other stresses. These observations of comparatively normal children under environmental difficulties have given Anna Freud material for important contributions.[21] The point that strikes the reader most emphatically is that separation from father and mother, especially the mother, is more devastating to the child than bombing. The author emphasizes the great importance of the first five years of life in the development of personality. "In the beginning of life the child is ruled merely by its own desires. It next learns to renounce gratifications for the sake of the parents . . . In the next phase it begins to share the parents' valuations." When it has learned to act on these new attitudes which were taken on because of love for the parent, "the child has established within itself a moral center—a conscience or superego." This transformation from primitive instinctive behavior to moral code seems to take place without effort or special knowledge in a secure, affectionate family setting. In residential nurseries or in other infant asylums, no matter how well run,

20. Freud, A.: An Introduction to the Technique of Child Analysis, Nervous and Mental Disease Monograph Series 48, New York, Nervous and Mental Disease Publishing Company, 1928.

21. Freud, A., and Burlingham, D.: Infants Without Families: The Case For and Against Residential Nurseries, New York, International Universities Press, 1944. Freud, A.: The Ego and the Mechanisms of Defense, translated by C. Baines, ibid., 1946.

this parental relationship is lacking, and the lack leads to pronounced disturbances.

René Spitz [22] has described a depressive syndrome that occurs in infants separated from their mothers. He cites cases in which children separated at 7 to 11 months of age soon became apprehensive, sleepless, weepy and withdrawn. They showed little interest in their environment and lost appetite and weight. Later retardation in development became obvious and the general picture of dejection might go on to stupor. If the mothers can be brought back within three months, the process is quickly reversed, with a return to normal. When the mother was away much longer, most of the children showed considerable retardation in bodily development, motor ability and speech. At 2 years of age only 5 out of 21 could walk. Some showed a picture of "stuporous catatonia"; 31 out of 91 children in one foundling home died in spite of apparently adequate hygiene and general care.

The mention of catatonia brings up the moot question of childhood schizophrenia. This has been long and carefully discussed, the most recent contribution being by Despert,[23] who gives a good summary and references. Children who present bizarre behavior, resembling what in an adult would certainly be diagnosed as schizophrenic, fortunately are rather rare. Large clinical centers, however, have collected impressive series of cases. The unanswered question is whether these children suffer from encephalopathy, from a congenital disorder, as some who use the term schizophrenia imply, or from a severe social maladjustment. The theory that they suffer from the last, at least in some cases, receives support from the work at the James J. Putnam Children's Center in Boston, directed by Beata Rank and Marian Putnam.[24] Here a meeting was held in November 1946 of the Child Psychiatry Committee of the American Society for Research in Psychosomatic Problems. At this meeting it was demonstrated that some children who showed grossly regressive behavior and seemed largely out of contact could be improved by intensive and prolonged psychotherapy in which the development of a warm relationship with the therapist and the use of play technics were the principle elements. Loss of the mother before the age of 2½ years seems to be an important cause or at least a precipitant of these regressive syndromes. Much more work is needed to improve diagnosis so that appropriate cases may be chosen for therapy. Long range follow-up

22. Spitz, R. A.: Anaclitic Depression, in Freud, A.; Hartmann, H., and Kris, E.: Psychoanalytic Study of the Child, New York, International Universities Press, Inc., 1946, vol. 2, p. 313.

23. Despert, J. L.: The Early Recognition of Childhood Schizophrenia, M. Clin. North America **31**:680, 1947.

24. Putnam, M. C.: Case Study of an Atypical Two-and-a-Half-Year-Old, Am. J. Orthopsychiat. **18**:1-30 (Jan.) 1948.

will be needed to see whether or not these children become schizophrenic later in life. But it looks as if at least some children could be benefited by psychologic means. Besides saving some children from a long life in hospitals for the mentally ill, this work might throw some light on the cause of schizophrenia. The work of Kempf,[25] Sullivan [26] and Rosen [27] indicates that some adult schizophrenics can be greatly improved by careful intensive and prolonged therapy. By this is meant getting down to the level of the patient and understanding his regressive ways and talk. A relationship with him is set up, and he is given support, so that he has a backing to throw off his great fear and inordinate sensitiveness. The treatment is strongly reminiscent of what has to be done for children with bizarre and regressive behavior.

A discussion of the even earlier relationship of mother and infant was organized by the Josiah Macy, Jr. Foundation on March 3 and 4, 1947, in New York.[28] Pediatric psychiatrists, psychologists and anthropologists met to talk about various aspects of the earliest relationships of parents and their offspring, especially the plan of having the infant continuously with its mother from the time of its birth. This is the "rooming-in" controversy that has been going on in obstetric hospitals. In the past twenty-five years the number of babies delivered in hospitals has increased enormously. It is the fashion to go to a hospital to have the baby delivered. Thus delivery, which is normally a physiologic event, has become a surgical procedure, with all that that implies in meticulous cleanliness and in restricted personal contacts. The baby is isolated and put on a strict regimen. "Rooming-in" is the reaction against all this. The child is left in the mother's room. She takes over its care as rapidly as she can and is instructed by the nurse in the necessary steps. The concensus was that from the psychologic standpoint rooming-in was advantageous. The anxiety of the mother was reduced, the baby was better cared for by being individualized, the transition from hospital to home was easier, the physician could observe the mother-child relationship better and the "rejecting" attitudes which may be developed in an orthodox obstetric regimen were avoided. The attitude of "training" is supplanted by one of permissive and affectionate care. Some interesting ethnologic observations on other races were brought in to support the thesis. One wonders how much memory the

25. Kempt, E. J.: Psychoanalytic Treatment of Dementia Praecox, Psychoanalyt. Rev. **6**:15-58, 1919.

26. Sullivan, H. S.: Conception of Modern Psychiatry, Psychiatry **3**:1-117 (Feb.) 1940 [pp. 69-82].

27. Rosen, J. N.: A Method of Resolving Acute Catatonic Excitement, Psychiatric Quart. **20**:183, 1946.

28. Senn, M. J. E.: Problems of Early Infancy, New York, Josiah Macy, Jr. Foundation, 1947.

infant can have of the events of the first ten days! It seems reasonable to suppose, however, that the sort of relationship started in these days between mother and child may be important in the future development of the child, especially in avoiding sensitiveness to fear and other harmful habit formations. Chisholm [29] goes so far as to say: "It is possible to bring up children who will in fact be able to live pleasantly and comfortably with other people without having to fight each other almost continuously as we and all our ancestors have always done." Saul [5] has a similar idea when he says: "No preventive step is more important than formulating our knowledge of aggression in the interests of diminishing this central threat to mankind."

### THE PYRAMIDAL TRACT AGAIN

Although the pyramidal tract and the cortical motor area was discussed at length in this review for 1945,[30] papers have since appeared which increase the understanding of the mechanism. Bosma and Gellhorn [31] showed in a series of experiments on monkeys that stimulation of a cortical focus results in definite patterns of movements if condensor discharges lasting ten seconds are used. This is long enough to permit facilitation, and it gives a more physiologic picture of what normally takes place. The popular method of brief threshold stimulation led to the erroneous theory that the cortex was made up of a mosaic of discrete points, each representing a definite unit of musculature. The principle of reciprocal innervation, with either inhibition of antagonists or cocontraction, was proved. The theories of Huhlings Jackson and the observations of Sherrington are thus substantiated for cortical function.

Walshe is at his polemic best in two papers in *Brain*. The first is "On the Notion of the 'Discrete Movement.'" [32] Here he points out that a discrete or isolated muscular movement is a physiologic impossibility. Voluntary movement is an enormously complex affair. The thesis that the pyramidal tracts innervate "discrete" or "isolated" movements and that the extrapyramidal tracts innervate complex postural movements is not tenable. The movements arising from the pyramidal system may differ in degree from those of the extrapyramidal system, but it is a quantitative and not a qualitative difference. The misunderstanding

29. Chisholm, B.: Revolutionary Changes in Sources of Security, Christian Register, August 1947, vol. 126.

30. Cobb, S.: Review of Neuropsychiatry for 1945, Arch. Int. Med. **77**:576 (May) 1946.

31. Bosma, J. F., and Gellhorn, E.: Organization of the Motor Cortex of the Monkey Based on Electroencephalographic Studies, Brain **70**:127, 1947.

32. Walshe, F. M. R.: On the Notion of the "Discrete Movement": A Critical Note, Brain **70**:93, 1947.

arises largely from the interpretation of experiments on stimulation, in which the motor and premotor areas of monkeys and other mammals were stimulated with new and refined technics. From the motor area brief twitches of part of a muscle have been recorded (never a single twitch similar to the reaction of a stimulated ventral horn cell). These short and localized responses have been interpreted as physiologic. There is reason to believe that they are not in any way similar to the normal contractions set up by the motor cortex. The electrical stimulus used in the laboratory experiments is so different from the normal excitation of the cortex that the experimenters should be much more cautious than they are in explaining cortical function on the basis of what they observe after applying the electrode. Walshe's exposition is clear, and his definition of terms is important. It is the use of ambiguous words that has led to much of the difficulty.

In the second paper [33] he reviews the evidence from animal experiments and from clinical observations and discusses the relation of the pyramidal system to the motor cortex, to the subordinate motor mechanisms and to the musculature. The higher levels of cortex employ the pyramidal system by way of short neurons to the motor area. This mechanism has to do with skilled movements including speech (eupraxia and euphasia). The motor area proper has its outlet directly through the pyramidal system. The cortical neurons are, of course, activated by afferent impulses, so the idea of a motor cortex controlling movement is fundamentally wrong. The masses of afferent impulses from thalamus and cortical sensory areas initiate and control the reactions of the motor cortex. It is a sensorimotor, reflex mechanism. It is closely associated, in both its afferent and its efferent aspects, with the basal ganglions and the cerebellum. Finally it plays on the motor cells of the spinal cord by way of a complex system of associated short neurons in the spinal gray matter. This makes it extremely unlikely that the pyramidal tract normally innervates single muscles. The thesis still holds that the cortex innervates movements and not muscles. In summary Walshe says:

> The pyramidal tract is an internuncial path, a common path, standing between the massed receptors on the one hand and the motor mechanisms of the nervous system on the other. It has evolved in particular relation to the development of the distance receptors, perhaps vision alone, and has reached its highest importance in man. It is the path by way of which the distance receptors put the motor mechanisms of the nervous system in operation; activate, and thereafter direct their action throughout the performance of those sequences of willed movement, short and long, simple and complex, characteristic of the normal organism. *The pyramidal system of itself initiates nothing, and to speak of it as*

33. Walshe, F. M. R.: On the Role of the Pyramidal System in Willed Movements, Brain **70**:329, 1947.

*'responsible for' this or that category of movements is to ignore the course and motive power of its activities. It is simply the channel through which pass the impulse volleys by which willed movement is activated and continuously moulded by controlling cortical afferent patterns of excitation.* If this be so, then it is concerned with all possible willed movements, and all aspects of willed movement, and if, as has been postulated, the cortex by way of the pyramidal system fractionates and then combines the functional elements of reflex segmental mechanisms, then every willed movement, short and long, small and large, restricted and ample, is as wholly pyramidal as it is extrapyramidal, and separate categories of movement thus anatomically classified or grouped as discrete or stereotyped have no existence as phenomena; they are abstractions not discernible as things or events in nature.

Adrian [34] in his Hughlings Jackson lecture draws similar conclusions from an entirely different set of data. From his refined study of nerve impulses, reverberating circuits and rhythmic activity, he comes to the conclusion that any nerve element in the afferent pattern leads to a change of central activity. He says:

Purposive acts must, therefore, be moulded like the movements of walking, by the controlling afferent patterns which are set up as the act progresses. The exciting disturbance may subside owing to fatigue or distraction, anything which will deflect our purpose; but the particular afferent pattern which signals accomplishment, the temporal and spatial distribution of sensory activity, must be uniquely related to the exciting pattern which it can dissipate. It must be in some way the inverse of the exciting pattern, the key that fits that particular lock. If this argument is valid it follows that one clue to the nature of the exciting pattern is to be sought in the nature of the afferent patterns which bring it to an end.

This brings in the important principle of "feed-back," a term borrowed from electrophysics, as are so many of our neurologic similes. In 1943 Rosenblueth, Weiner and Bigelow [35] wrote their classic paper on this subject. They rescued teleology from its scientific unpopularity, arguing that purposeful activity is the most important kind of behavior since it makes room for volition. "Feed-back" is the mechanism that makes this possible. In physiology it means that the behavior is controlled by sensory impulses that come back to the organism as a result of the behavior. "The behavior of an object is controlled by the margin of error at which the object stands, at a given time, with reference to a relatively specific goal. The feed-back signals from the goal are used to restrict outputs which would otherwise go beyond the goal." All purposeful behavior requires this sort of feed-back. It is obviously important in such functions as that of the cerebellum. It is also essential to intelligent behavior at higher levels. Predictive extrapolations

34. Adrian, E. D.: General Principles of Nervous Activity, Brain **70**:1, 1947.

35. Rosenblueth, A.; Weiner, N., and Bigelow, J.: Behavior, Purpose and Teleology, Philos. of Sc. **10**:18, 1943.

would be impossible without it, and these are the basis of intelligence. Thorndike [36] has shown a similar mechanism to be important in learning. It signals back to the brain of the organism the satisfyingness of the reaction which is confirmed or not. Confirmation makes the reaction take place more easily next time. If such neurologic mechanisms can be proved (and the evidence for them is good) science can take a step forward out of its fatalism and make room for such concepts as choice and volition.

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36. Thorndike, E. L.: Man and His Works, (William James Lectures, 1942-1943), Cambridge, Mass., Harvard University Press, 1943.

# CARDIOVASCULAR DISEASES

## A Review of Significant Publications From January 1944 to June 1947

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*(Concluded from Page 238)*

### CORONARY HEART DISEASE

The predilection of atherosclerosis for the coronary arteries is the subject of a paper by Dock [126] which provides much food for thought. Dock points out that atheromatosis may be limited to the coronary arteries, without evident involvement of other portions of the vascular system and that this is the rule in coronary heart disease in men under 40. He discusses the role of hypercholesteremia, pointing out that there is a high incidence of coronary artery disease in congenital xanthomatosis and also in other conditions in which there is a high blood cholesterol level, as in obesity, diabetes mellitus and myxedema. He also refers to the possibility that the increased incidence of myocardial infarction in hypertensive persons may be due to the greater oxygen needs of the left ventricle as well as to a greater severity of atherosclerosis. In his studies of the intima of the coronary arteries of newborn infants Dock found that the male begins life with a coronary intima three times as thick as that of the female, this thickening being present only in the epicardial branches of the coronary arteries. He considers the possibility that despite this natural endowment of the male sex no coronary atherosclerosis need occur if no hypertension ensues and if cholesterol metabolism is efficient.

The role of cholesterol in coronary heart disease was investigated by Shaffer,[127] who compared a series of 100 patients with duodenal ulcer (who had been on a diet presumably rich in cholesterol for five or more years) with a group of 500 controls of the same age and sex ratio without known ulcer or endocrinopathy. He noted the same incidence of myocardial infarction (3 per cent) in the two groups and concluded that the role of cholesterol in the pathogenesis of coronary heart disease is doubtful. It should be pointed out that exact information as to the

126. Dock, W.: The Predilection of Atherosclerosis for the Coronary Arteries, J. A. M. A. **131**:875 (July 13) 1946.

127. Shaffer, C. F.: Nutritional Rôle of Cholesterol in Human Coronary Arteriosclerosis, Ann. Int. Med. **20**:948, 1944.

diet of these two groups was not available. Furthermore, a large oral cholesterol intake does not necessarily produce an increase in the cholesterol deposits in the body, as this compound is broken down in the process of digestion and absorption in the gastrointestinal tract.

Wilens [128] has attacked this problem from a different point of view. He has reviewed the reports of necropsy on 1,250 persons aged 35 or over, using the admittedly rather unreliable estimate of the state of nutrition of the body and of the presence of atherosclerosis as indicated in the protocols. As he points out, loss of weight due to terminal illness tended to reduce rather than exaggerate any differences in the incidence of atherosclerosis which might be related to the original state of nutrition. His statistics reveal that the incidence of atherosclerotic disease was higher in obese persons than in those who were poorly nourished; for example, in 169 obese men the incidence of advanced atherosclerosis was 40 per cent as compared with an incidence of 16 per cent in 367 men who were considered to be poorly nourished. Wilens believes that the frequency of this type of vascular disorder is higher in young obese persons than in old ones and that the relationship between atherosclerosis and the state of nutrition is independent of sex, hypertension, weight of the heart and diabetes.

One may justifiably view with alarm the increasing number of reports of fatal coronary heart disease in young persons. Scott and Miller [129] report a case of fatal coronary thrombosis in an infant 11 months of age, and French and Dock,[130] Poe [131] and Richards [132] report fatal myocardial infarction in persons between the ages of 19 and 40. French and Dock stress the fact that 91 per cent of a group of 80 young soldiers who died of coronary heart disease were overweight. They report that vigorous effort and activity of early morning chores brought on fatal attacks in over 50 per cent of their cases. In this regard Blumgart,[133] citing 11 examples of acute myocardial infarction related to effort, states that the pathologic mechanisms involved may be subintimal hemorrhages, rupture of an atheromatous abscess or relative ischemia brought on by exertion.

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128. Wilens, S. L.: A Study on the Bearing of General Nutritional State to Atherosclerosis, Arch. Int. Med. **79**:129 (Feb.) 1947.

129. Scott, E. P., and Miller, A. J.: Coronary Thrombosis: Report of a Case in an Infant Eleven Months of Age, J. Pediat. **28**:478, 1946.

130. French, A. J., and Dock, W.: Fatal Coronary Arteriosclerosis in Young Soldiers, J. A. M. A. **124**:1233 (April 29) 1944.

131. Poe, W. D.: Fatal Coronary Artery Disease in Young Men, Am. Heart J. **33**:76, 1947.

132. Richards, G. A.: A Case of Coronary Thrombosis with Myocardial Infarction in a Nineteen Year Old White Male, Ann. Int. Med. **24**:908, 1946.

133. Blumgart, H. L.: The Relation of Effort to Attacks of Acute Myocardial Infarction, J. A. M. A. **128**:775 (July) 1945.

A comprehensive study of the clinical aspects of pain in the chest has been undertaken by Harrison.[134] An analysis of the symptoms of 77 patients with angina pectoris reveals certain interesting facts. For example, 11 patients who had pain on effort also complained of the same symptom on lying down; in some, swallowing and eating precipitated pain, and relief was at times obtained by the ingestion of food, vomiting, belching or the expulsion of flatus. Spontaneous hypoglycemia, paroxysmal dyspnea and paroxysmal tachycardia were among the initiating nocturnal factors. Harrison refers to apparent recovery from angina pectoris in 12 of his patients, 4 being relieved of their symptoms after a coronary occlusion, 3 after hypoglycemia or anemia had been controlled and 5 without apparent cause (it may be assumed that an adequate collateral circulation had developed). In all, 10 per cent of his patients had anginal pain unrelated to effort. It is, of course, possible that some of the patients whom he describes were suffering either from a condition other than coronary heart disease or from coronary heart disease plus an associated gastrointestinal or other lesion, since pathologic proof of the existence of coronary sclerosis or disease of the aortic valve was not available in the majority of his cases. The same author has considered the problem of pain arising in both the esophagus and the stomach, pointing out that either of these types may mimic angina pectoris even to the radiation of pain to the left shoulder and arm. He calls attention to the fact that nitroglycerin may relieve esophageal and gastric pain, although usually not so effectively as it does in coronary insufficiency. Josey and Murphey[135] remind us that the differential diagnosis of angina pectoris should include rupture of a cervical intervertebral disk.

The use of tests designed to assist in the diagnosis of coronary heart disease has been the subject of numerous papers during recent years. Indeed, it would appear that both the exercise and the anoxemia tests are probably receiving a wider use than is necessary. Master, Huzie, Brown and Parker[136] have compared the "two-step" exercise test with the Levy anoxemia test (which utilizes inhalation of a 10 per cent oxygen and a 90 per cent nitrogen mixture). It is the conclusion of these authors from studies on 84 navy personnel that the results of the two procedures were almost identical. They believe, however, that the anoxemia test is more severe and causes more of a reaction than does the exercise test in addition to being a procedure which requires special

134. Harrison, T. R.: Clinical Aspects of Pain in the Chest: I. Angina Pectoris, Am. J. M. Sc. **207**:561, 1944; II. Pain Arising in the Esophagus, ibid. **209**:765 1945; III, Pain Arising from the Stomach, ibid. **209**:771, 1945.

135. Josey, A. I., and Murphey, F.: Ruptured Intervertebral Disk Simulating Angina Pectoris, J. A. M. A. **131**:581 (June 15) 1946.

136. Master, A. M.; Huzie, S.; Brown, R. C., and Parker, R. C., Jr.: The Electrocardiogram and the "Two-Step" Exercise, Am. J. M. Sc. **207**:435, 1944.

equipment. Biörck [137] in Stockholm has likewise employed both tests and although he believed that the anoxemia test was of greater diagnostic value than was the use of exercise he found that the majority of patients who inhaled the 10 per cent oxygen and 90 per cent nitrogen mixture became cyanotic and that many got a severe headache. He also described shock in 2 cases. It is his conclusion that care must be used in the interpretation of negative reactions to tests.

A study has been reported by Weintraub and Bishop,[138] who used the anoxemia procedure on 200 controls and on 20 patients with known angina pectoris on effort. It was noted that 2 of the patients with coronary heart disease had neither pain nor positive electrocardiographic changes while in the oxygen-poor atmosphere. Of the 200 controls, none had pain but 9 showed electrocardiographic changes. Unpleasant reactions included restlessness, air hunger, headache, pain in the chest and clonic tremors, and of the total 220 patients, 8 had severe reactions. The use of the anoxemia test has also been described by Pruitt, Burchell and Barnes,[139] who list thirty-nine unfavorable reactions in two hundred and eighty-nine tests. Four of their patients temporarily lost consciousness, 9 appeared on the verge of shock and 2 more experienced cardiac arrest for a brief period. The occurrence of pain alone during this test was considered to be an unreliable indication of the presence of coronary heart disease. They state in summary: "Use of the anoxia test should be restricted even among acceptable cases to instances in which (1) serious disagreement regarding diagnosis has occurred, and (2) the establishment of a definite diagnosis is of such importance that acquisition of all helpful evidence is imperative." This view would indeed appear to be a sensible one. The use of low oxygen tests to determine the myocardial reserve of children, as described by Mannheimer,[140] appears to have little to recommend it.

The prognostic significance of auricular fibrillation in association with myocardial infarction was studied at the Los Angeles County General Hospital by Askey and Neurath.[141] They found the mortality among a group of 1,247 patients with myocardial infarction to be 51.5 per cent. The mortality in a group of 84 patients with auricular fibril-

137. Biörck, G.: Hypoxaemia Tests in Coronary Disease, Brit. Heart J. **8**: 17, 1946; Anoxemia and Exercise Tests in the Diagnosis of Coronary Disease, Am. Heart J. **32**:689, 1946.

138. Weintraub, H. J., and Bishop, L. F., Jr.: The Anoxemia Test for Coronary Insufficiency, Ann. Int. Med. **26**:741, 1947.

139. Pruitt, R. D.; Burchell, H. B., and Barnes, A. R.: The Anoxia Test in the Diagnosis of Coronary Insufficiency: Study of Two Hundred and Eighty-Nine Cases, J. A. M. A. **128**:839 (July 21) 1945.

140. Mannheimer, E.: The Hypoxia Tolerance Test of the Heart in Children, J. Pediat. **29**:329, 1946.

141. Askey, J. M., and Neurath, O.: The Prognostic Significance of Auricular Fibrillation in Association with Myocardial Infarction, Am. Heart J. **29**:575, 1945.

lation (selected from the same series) was 79.8 per cent, however, and the percentage of deaths was even higher when the arrhythmia preceded the infarction; the mortality was likewise higher with persistent fibrillation than with transient fibrillation.

As with congestive heart failure, there has been interest in the necessity for restriction of activity and the effect on the recovery rate and on the healing process in the treatment of myocardial infarction. Using rats as their experimental animals, Thomas and Harrison [142] produced an area of myocardial damage on the left ventricular surface by actual searing of the muscle. They then divided their animals into several groups; one of the groups exercised as desired, the second were given the optional use of a treadmill, the third were made to take exercise (swimming) and the fourth had their activity restricted by snug-fitting cages. Of 49 rats whose activity was limited, 34 died at the end of three months (the immediate postoperative deaths are excluded); only 18 of 47 animals who exercised as they desired died. There was no evidence that animals forced to exercise did well or, indeed, poorly as a group. While the authors recognize that such experimental data may have a limited application to clinical problems, they suggest that strict rest in bed for the first two weeks of recovery from infarction may be all that is desired. They did observe that when cardiac rupture occurred in their animals it came usually during the second week. Of great significance in this respect is the work of Friedman and White,[143] and that of Jetter and White,[144] who found an incidence of rupture in the heart of only 9 per cent in 105 patients with acute myocardial infarction studied pathologically at the Massachusetts General Hospital and an incidence of 73 per cent among 22 patients with acute infarction studied pathologically in Massachusetts mental institutions. In the latter group restriction of activity had not been employed because of the obvious difficulties in diagnosis. It was found that death always ensued rapidly after the episode of rupture and that all deaths occurred within two weeks of the onset of infarction. No healed infarcts were found to have ruptured. Certainly these statistics point to the wisdom of at least a fortnight's rest in bed after myocardial infarction.

The question of the use of anticoagulants in the treatment of coronary heart disease is a matter of recent investigation. Meyers and Poindexter [145] have found that the prothrombin time appears to shorten

142. Thomas, W. C., and Harrison, T. R.: The Effect of Artificial Restriction Of Activity on the Recovery of Rats from Experimental Myocardial Injury, Am. J. M. Sc. **208**:436, 1944.

143. Friedman, S., and White, P. D.: Rupture of the Heart in Myocardial Infarction: Experience in a Large General Hospital, Ann. Int. Med. **21**:778, 1944.

144. Jetter, W. W., and White, P. D.: Rupture of the Heart in Patients in Mental Institutions, Ann. Int. Med. **21**:783, 1944.

145. Meyers, L., and Poindexter, C. A.: A Study of the Prothrombin Time in Normal Subjects and in Patients with Arteriosclerosis, Am. Heart J. **31**:27, 1946.

nocturnally in patients with coronary artery disease (they studied only 6 normal controls and 10 patients with coronary heart disease). These authors also found a definite trend toward shortening of prothrombin time in 13 patients with acute coronary occlusion and noted that this change preceded the use of digitalis (which was employed in 5 cases) and that the abnormality lasted for several weeks. The test which they employed made use of both diluted and undiluted plasma. Similar studies, using the heparin-retarded clotting test in patients suffering from acute coronary thrombosis, have been reported by Ogura and his associates.[146] While conceding that the laboratory evidence which they obtained was not an infallible guide, they concluded that an acceleration of the blood coagulation occurred usually by the second or third day in 78 per cent of 27 cases so studied and lasted to about the seventeenth day. Reviewing the incidence of embolic or thrombotic processes during the immediate convalescence from acute myocardial infarction, Nay and Barnes[147] found that in 100 such patients (none of whom received anticoagulants) there were episodes of a second myocardial infarction in 15, episodes of pulmonary embolism in 14, cerebrovascular accidents in 8, thrombophlebitis in 7 and peripheral arterial occlusion in 4.

These investigations have naturally led to the use in certain clinics of anticoagulants in the treatment of acute coronary heart disease. Wright[148] has reported on the use of "dicumarol" in 76 patients with coronary thrombosis who had had multiple thrombi or repeated embolic phenomena and in 33 patients with uncomplicated coronary thrombosis. In his series 15 patients succumbed, 11 from heart failure and 4 as a direct, immediate result of the "insult of thrombosis." It is his belief that "dicumarol" is of value in the prevention of these complications which Nay and Barnes described, and he advises its use for thirty days after the last episode of thrombosis or embolism. In his series there were no serious toxic results from the use of the drug, but he stresses the fact that the prothrombin level must be determined before the daily dose of the drug is administered. Peters, Guyther and Brambel[149] and Nichol and Page[150] have similarly been encouraged

146. Ogura, J. H.; Fetter, N. R.; Blankenhorn, M. A., and Glueck, H. I.: Changes in Blood Coagulation Following Coronary Thrombosis Measured by the Heparin Retarded Clotting Test (Waugh and Ruddick Test), J. Clin. Investigation **25**:586, 1946.

147. Nay, R. M., and Barnes, A. R.: Incidence of Embolic or Thrombotic Processes During the Immediate Convalescence from Acute Myocardial Infarction, Am. Heart J. **30**:65, 1945.

148. Wright, I. S.: Experiences with Dicumarol (3, 3′ Methylene-Bis-[4-Hydroxycoumarin]) in the Treatment of Coronary Thrombosis with Myocardial Infarction, Am. Heart J. **32**:20, 1946.

149. Peters, H. R.; Guyther, J. R., and Brambel, C. E.: Dicumarol in Acute Coronary Thrombosis, J. A. M. A. **130**:398 (Feb. 16) 1946.

150. Nichol, E. S., and Page, S. W.: Dicumarol Therapy in Acute Coronary Thrombosis, J. Florida M. A. **32**:365, 1946.

by their results with this form of treatment in acute coronary heart disease. Nichol [151] does, however, refer to 1 patient who died from a cerebral hemorrhage, attributable probably to the "dicumarol." These reports are of great interest, but still further work is required before the general use of anticoagulants in this type of heart disease can be recommended. It should be emphasized once again that careful laboratory observation of the prothrombin level is essential.

Brief mention may be made of recent reports on the use of certain other drugs in coronary artery disease. Mokotoff and Katz [152] studied the hearts of a series of 46 dogs in which the left anterior descending coronary artery had been ligated eight weeks previously. Subsequently they had treated one third of the animals with aminophylline and one third with papaverine hydrochloride, and the remaining third had been kept as controls. These investigators noted that the hearts of the dogs who had received either of the two drugs employed showed smaller infarcts than did the hearts of the control group. Papaverine hydrochloride seemed to be somewhat superior to aminophylline in this regard. Riseman and his associates [153] have appraised the value of alcohol, papaverine hydrochloride and cobra venom in patients with angina pectoris who were subjected to a standardized exercise tolerance test. Their results indicated that alcohol was of relatively little value except to promote a sense of well-being and that papaverine hydrochloride given intravenously had a definite but brief beneficial effect (oral administration was ineffective) but that cobra venom given intramuscularly was of distinct benefit in 7 of 12 patients with angina pectoris and, in particular, in 4 of 5 patients who did not respond to conventional therapy. They also observed that papaverine hydrochloride given by the intravenous route afforded considerable relief of pain when myocardial infarction was present.

Proger and Dekaneas [154] have endeavored to combat myocardial anoxia by enhancing the tissue uptake of oxygen by the intravenous use of cytochrome C. In a small group of cases of coronary heart disease they found that this drug could prevent the appearance of electrocardio-

151. Nichol, E. S.: Treatment of Acute Coronary Thrombosis with Dicumarol: Further Observations, Am. Heart J. **33**:722, 1947.

152. Mokotoff, R., and Katz, L. N.: The Effect of Theophyllin with Ethylenediamine (Aminophylline) and of Papaverine Hydrochloride on Experimental Myocardial Infarction in the Dog, Am. Heart J. **30**:215, 1945.

153. Gray, W.; Riseman, J. E. F., and Stearns, S.: Papaverine in the Treatment of Coronary Artery Disease, New England J. Med. **232**:389, 1945. Freedberg, A. S., and Riseman, J. E. F.: Cobra Venom in the Treatment of Angina Pectoris, ibid. **233**:462, 1945. Stearns, S.; Riseman, J. E. F., and Gray, W.: Alcohol in the Treatment of Angina Pectoris, ibid. **234**:578, 1946.

154. Proger, S., and Dekaneas, D.: Some Effects of Injected Cytochrome C in Myocardial and Cerebral Anoxia in Man, J. Pediat. **29**:729, 1946.

graphic changes accompanying the Levy anoxemia test for coronary insufficiency. The preparation did not appear to be more than moderately effective in increasing capacity for physical exertion in patients with angina pectoris, however, and had no effect in acute myocardial infarction. It is not surprising that the consequences of a "medical thyroidectomy" by the use of thiouracil in patients with coronary heart disease should be the subject of several reports in view of earlier enthusiasm for surgical ablation of the thyroid gland. Raab [155] was impressed with the beneficial effects of thiouracil in 10 patients with angina, and Ben-Asher [156] concluded that 67 per cent of a series of 37 of his patients were improved by its administration. DiPalma and MaGovern,[157] on the other hand, were disappointed in its use and described the disadvantages attending prolonged ingestion of the drug. In view of the spontaneous remissions which are known to occur with angina pectoris and the lack of adequate controls in the series just mentioned as well as the previous unfavorable experiences with surgical thyroidectomy, it would appear that thiouracil has little place in the armamentarium employed routinely in the therapy of coronary heart disease. Further studies [158] on the use of testosterone in angina pectoris have likewise failed to confirm the value of this hormonal preparation, and vitamin E, the use of which has received considerable premature publicity, has been the subject of a recent sobering editorial [159] which points to the need of further careful evaluation.

Finally, reference should be made to surgical measures which have been described for the relief of intractable coronary pain. White,[160] in summarizing his experiences with paravertebral injection of alcohol in the upper thoracic sympathetic ganglions, has reported excellent results in 56 per cent and 8 operative deaths in 8 per cent of 75 cases; postoperative intercostal neuralgia was a serious complaint in 10 per cent of the series. Of another group of 8 patients who were subjected to sympathectomy performed in the upper thoracic area, 4 were described as having excellent relief for more than one year and 3 others did well temporarily until their demise within twelve months of operation. The

155. Raab, W.: Thiouracil Treatment of Angina Pectoris: Rationale and Results, J. A. M. A. **128**:249 (May 26) 1945.

156. Ben-Asher, S.: Further Observations on the Treatment of the Anginal Syndrome with Thiouracil, Am. Heart J. **33**:490, 1947.

157. DiPalma, J. R., and MaGovern, J. J.: Disadvantages of Thiouracil Treatment of Angina Pectoris, Am. Heart J. **32**:494, 1946.

158. Levine, E. B., and Sellers, A. L.: Testosterone in Angina Pectoris, Am. J. M. Sc. **212**:7, 1946.

159. Vitamin E and Heart Disease, Current Comment, J. A. M. A. **131**:746 (June 29) 1946.

160. White, J. C.: The Surgical Relief of Severe Angina Pectoris, Bull. New England M. Center **9**:1, 1947.

relief of angina by the drastic procedure of pericoronary neurectomy combined with ligation of the great cardiac vein has been reported by Fauteux as successful in 1 patient.[161] Of 10 other patients for whom surgical treatment was limited to ligation of the great cardiac vein, 7 received some benefit and 1 died.

### PULMONARY HEART DISEASE

The recording of the pressure of the right side of the heart in patients with chronic pulmonary disease has been accomplished by Bloomfield,[162] working with Cournand and his associates. By means of cardiac catheterization the authors demonstrated that an extreme degree of pulmonary emphysema or fibrosis might exist with little if any evidence of strain on the right side of the heart as revealed by this technic. The whole subject of chronic cor pulmonale has been reviewed by Spain and Handler,[163] who studied 60 cases from the files of the Bellevue Hospital in New York city. After summarizing the clinical features in this group of cases, these writers concluded that the primary cause of cor pulmonale was not obliteration of the pulmonary vascular bed, fibrosis of the lungs or the influence of polycythemia but rather the result of the changed pressure relation within the alveoli producing an increased resistance to the flow of blood. They point out that the term emphysema does not necessarily imply an associated pulmonary fibrosis.

The interesting condition of thrombosis of the pulmonary veins has been discussed by Spain and Moses.[164] These authors recorded 15 cases in which there was associated embolism to the arterial system, including the kidneys and the spleen. Twelve of the patients showed extensive pulmonary tuberculosis, for 1 the diagnosis of bronchiogenic carcinoma was made, 1 had bronchiectasis and only 1 showed no pathologic changes other than pulmonary infarction.

It is not the function of this review to discuss peripheral vascular disease. Mention should be made, however, of the recent extensive literature relating to venous thrombosis and pulmonary embolism since

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161. Fauteux, M.: Treatment of Coronary Disease with Angina by Pericoronary Neurectomy Combined with Ligation of the Great Cardiac Vein, Am. Heart J. **31**:260, 1946.

162. Bloomfield, R. A.; Lauson, H. D.; Cournand, A.; Breed, E. S., and Richards, D. W., Jr.: Recording of Right Heart Pressures in Normal Subjects and in Patients with Chronic Pulmonary Disease and Various Types of Cardiocirculatory Disease, J. Clin. Investigation **25**:639, 1946.

163. Spain, D. M., and Handler, B. J.: Chronic Cor Pulmonale: Sixty Cases Studied at Necropsy, Arch. Int. Med. **77**:37 (Jan.) 1946.

164. Spain, D. M., and Moses, J. B.: Thrombosis and Embolism of Pulmonary Vessels with Special Reference to Pulmonary Vein Thrombosis, Am. J. M. Sc. **212**:707, 1946.

this condition is frequently encountered in patients with cardiac disease. As Carlotti and his associates [165] have pointed out, there is actually a greater incidence of pulmonary embolism among medical patients than among surgical patients, with the majority of the former suffering from heart disease. There is some difference of opinion as to the best form of treatment for the patient who exhibits either phlebothrombosis or thrombophlebitis. Allen, Linton and Donaldson [166] recommend ligation of the superficial femoral veins bilaterally as the treatment of choice in established phlebothrombosis and in early thrombophlebitis, and they also suggest the wisdom of prophylactic ligation of the veins in aged and debilitated patients. Ochsner [167] agrees that surgical intervention is indicated when phlebothrombosis is present but states that venous ligation is rarely necessary in the treatment of uncomplicated thrombophlebitis. The use of anticoagulants instead of surgical measures has been advocated by several writers. Heparin has been recommended by Loewe and Hirsch [168] and by Bauer [169] as being an effective form of therapy in the presence of venous thromboembolic disease, and the combined use of heparin and "dicumarol" or use of the latter alone has been described by Allen,[170] of the Mayo Clinic, and others. The statistics which these various writers have published can be obtained from their original articles, but it is perhaps fair to say that good results appear to have been secured both by surgical treatment and by the use of anticoagulants.

Two further reports [171] of fatalities resulting from the administration of morphine to patients with kyphoscoliosis and kyphoscoliotic heart disease call attention once again to the lethal effects of even minute doses of this drug when an extremely reduced pulmonary reserve is present. The conclusion that morphine is contraindicated in this condition (as are all narcotics) may also be applied to severe chronic pulmonary disease in general.

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165. Carlotti, J.; Hardy, I. B., Jr.; Linton, R. R., and White, P. D.: Pulmonary Embolism in Medical Patients, Am. Heart J. **33**:737, 1947.

166. Allen, A. W.; Linton, R. R., and Donaldson, G. A.: Venous Thrombosis and Pulmonary Embolism, J. A. M. A. **133**:1268 (April 26) 1947.

167. Ochsner, A.: Venous Thrombosis, J. A. M. A. **132**:827 (Dec. 7) 1946.

168. Loewe, L., and Hirsch, E.: Heparin in the Treatment of Thromboembolic Disease, J. A. M. A. **133**:1263 (April 26) 1947.

169. Bauer, G.: Heparin Therapy in Acute Deep Venous Thrombosis, J. A. M. A. **131**:196 (May 18) 1946.

170. Allen, E. V.: The Clinical Use of Anticoagulants: Report of Treatment with Dicumarol in 1,686 Postoperative Cases, J. A. M. A. **134**:323 (May 24) 1947.

171. Daley, R.: Morphine Hypersensitivity in Kyphoscoliosis, Brit. Heart J. **7**:101, 1945. Katz, K. H., and Chandler, H.: Morphine Hypersensitivity in Kyphoscoliotic Heart Disease, read at meeting of New England Heart Association, January 1946.

### OTHER CARDIOVASCULAR CONDITIONS

While the treatment of cardiovascular syphilis with penicillin has been introduced too recently for a seasoned evaluation comparable to that made after experience over several decades with iodides, bismuth and arsenicals, it is nevertheless of interest to review those cases of cardiovascular syphilis in which the new form of therapy has been used. Russek, Cutler, Fromer and Zohman [172] treated 15 patients with syphilitic aortitis (4 of them with aneurysms) on a dose schedule of 40,000 units of penicillin intramuscularly every two hours until a total of 3,400,000 units had been given. The authors state that 4 of their patients showed definite improvement and that only 1 experienced mild substernal pain. No serious toxic reactions occurred.

Among descriptions of still other diseases which are found to affect the heart, Gore [173] has reviewed 1,402 cases of myocarditis recorded at the Army Institute of Pathology during World War II and has listed myocardial involvement associated with syphilis, scarlet fever, diphtheria, acute meningococcemia, scrub typhus, tuberculosis, epidemic hepatitis and many other diseases.[174] An excellent study of 2 patients who succumbed to acute myocarditis due to infection with influenza A has been reported by Finland and his colleagues,[175] and fatalities from cardiac disease secondary to cutaneous diphtheria have been described by Kay and Livingood [176] and by Solomon and Irwin.[177] Other writers [178] have described meningococcic myocarditis and myocarditis in children associated with acute laryngotracheobronchitis. Electrocardiographic evidence of cardiac complications in infectious mononucleosis has been reported by Evans and Graybiel [179] and in mumps by Wendkos and

172. Russek, H. I.; Cutler, J. C.; Fromer, S. A., and Zohman, B. L.: Treatment of Cardiovascular Syphilis with Penicillin, Ann. Int. Med. **25**:957, 1946.

173. Gore, I.: Mocarditis in Infectious Diseases, Am. Pract. **1**:292, 1947.

174. Seventy per cent of the patients who died from syphilis or from scarlet fever showed demonstrable myocarditis, and myocarditis was found in 100 per cent of the cases of acute meningococcemia and scrub typhus.

175. Finland, M.; Parker, F., Jr.; Barnes, M. W., and Joliffe, L. S.: Acute Myocarditis in Influenza A Infections, Am. J. M. Sc. **209**:455, 1945.

176. Kay, C. F., and Livingood, C. S.: Myocardial Complications of Cutaneous Diphtheria, Am. Heart J. **31**:744, 1946.

177. Solomon, S., and Irwin, C. W.: Cutaneous Diphtheria with Toxic Myocarditis: Report of a Fatal Case with Necropsy Findings, Ann. Int. Med. **26**: 116, 1947.

178. Holman, D. V., and Angevine, D. M.: Meningococcus Myocarditis, Am. J. M. Sc. **211**:129, 1946. Saphir, O.: Laryngeal Edema, Myocarditis and Unexpected Death (Early Acute Laryngotracheobronchitis), ibid. **210**:296, 1945.

179. Evans, W. F., and Graybiel, A.: Electrocardiographic Evidence of Cardiac Complications in Infectious Mononucleosis, Am. J. M. Sc. **211**:220, 1946.

Noll,[180] and abnormalities of the electrocardiogram occurring during pneumococcic pneumonia have been summarized by Thomson and his associates.[181] The importance of the myocardial involvement in South American trypanosomiasis (Chagas' disease) has been well indicated by Moseley and Miller[182] in a recent review of this disease. Most physicians who live in North America are little aware of the frequency and severity of the cardiac involvement in this interesting condition which may closely simulate coronary heart disease both in its symptoms and in its electrocardiographic changes.

Finally, mention should be made of the report by Levy and von Glahn[183] of a group of 10 patients with cardiac hypertrophy of unknown cause. Their series adds 10 more cases to those described by other writers during the past four years. Although it does not throw further light on the etiology of this mysterious disease, it presents a good summary of the clinical and pathologic findings. It is of interest that 2 of their patients had positive Wassermann reactions. These authors found that arterial embolism from mural thrombi was a frequent occurrence, the lungs being involved six times, the kidneys four times and the spleen and the retina once each. All their patients died, 7 from progressive myocardial insufficiency and the remaining 3 from sudden death attributable to heart disease. In no instance was there evidence of avitaminosis. At autopsy the coronary arteries showed a striking absence of advanced sclerosis; myocardial hypertrophy was invariably present (with associated necrosis and fibrosis in 4 of the cases), and mural thrombi were present in 6 instances. The valves of the heart were normal.

Fletcher[184] has studied the cardiac output in a case of pericardial effusion and has found that despite the presence of cardiac tamponade the effective right auricular filling pressure and the cardiac output were within normal limits. He suggests that it may be only in the agonal stage of tamponade that the pericardial pressure approaches the venous pressure and the cardiac output falls. Changes in the circulation in constrictive pericarditis have been investigated by Lyons and Burwell,[185]

180. Wendkos, M. H., and Noll, J.: Myocarditis Caused by Epidemic Parotitis, Am. Heart J. **27**:414, 1944.

181. Thomson, K. J.; Rutstein, D. D.; Tolmach, D. M., and Walker, W. H.: Electrocardiographic Studies During and After Pneumococcus Pneumonia, Am. Heart J. **31**:565, 1946.

182. Moseley, V., and Miller, H.: South American Trypanosomiasis (Chagas' Disease), Arch. Int. Med. **76**:219 (Oct.) 1945.

183. Levy, R. L., and von Glahn, W. C.: Cardiac Hypertrophy of Unknown Cause, Am. Heart J. **28**:714, 1944.

184. Fletcher, C. M.: Cardiac Output in a Case of Pericardial Effusion, Brit. Heart J. **7**:143, 1945.

185. Lyons, R. H., and Burwell, C. S.: Induced Changes in the Circulation in Constrictive Pericarditis, Brit. Heart J. **8**:33, 1946.

who have stated the belief that the principal circulatory defect is limitation of the diastolic filling of the ventricles, which results in a diminshed output per beat. Unlike the normal heart, the heart with a constricting pericardium fails to increase its output per beat or its rate in the presence of a spontaneous or an induced rise in venous pressure. They noted that spontaneous increases in rate were associated with a reduced output per beat but with a slight increase in the total output per minute. Zimmerman and Durgin [186] have reported on a 27 year old Negro with septicemia and pericarditis caused by Staphylococcus aureus who had been treated with sulfadiazine without benefit. The authors then administered 10,000 units of penicillin intrapericardially, giving the drug intramuscularly and intravenously as well, with excellent clinical results and eventual cure.

The effect of posture on the auriculoventricular conduction time has been the subject of three reports. Holmes and Weill [187] have described 2 patients whose P-R interval became prolonged when they were recumbent; the interval returned to normal with a change to the erect position. Four of 20 patients with defective auriculoventricular conduction studied by Manning and Stewart [188] were similarly affected by changes in posture, and Stein [189] has reported a case in which the patient had complete heart block when recumbent and high grade first degree block when sitting. The treatment of 8 patients with ventricular tachycardia with large doses of quinidine sulfate has been reviewed by Zimmerman.[190] Seven of his patients recovered, and 1 died from a massive anterior myocardial infarction. This author disregarded toxicity from quinidine as evidenced by prolongation of the intraventricular conduction time, believing that the use of the drug is essential despite such a finding.

Askey [191] has collected the clinical data on 7 patients in whom hemiplegia developed after stimulation of the carotid sinus. It was of interest that no patient was under 42 years of age and that the hemiplegia was invariably on the side opposite to that on which pressure had been exerted; the neurologic damage was transient or minimal in

186. Zimmerman, J. J., and Durgin, B.: Staphylococcus Aureus Septicemia and Pericarditis Treated with Penicillin, Am. Heart J. **31**:93, 1946.

187. Holmes, J. H., and Weill, D. R., Jr.: Incomplete Heart Block Produced by Changes in Posture, Am. Heart J. **30**:291, 1945.

188. Manning, G. W., and Stewart, C. B.: Alteration in P-R Interval Associated with Change in Posture, Am. Heart J. **30**:109, 1945.

189. Stein, I.: Postural Heart Block, Am. J. M. Sc. **212**:604, 1946.

190. Zimmerman, S. L.: Ventricular Tachycardia—A Report of Ten Cases, Eight of Which Were Treated with Quinidine with Recovery in Seven, Ann. Int. Med. **23**:634, 1945.

191. Askey, J. M.: Hemiplegia Following Carotid Sinus Stimulation, Am. Heart J. **31**:131, 1946.

all cases. He advises that considerable caution be exercised in the use of stimulation of the carotid sinus in elderly or middle-aged persons. The whole subject of the hyperactive cardioinhibitory carotid sinus reflex has been reviewed by Nathanson,[192] who calls attention to the fact that over 65 per cent of 115 patients who demonstrated this condition had no related symptoms. For those persons who have characteristic complaints Nathanson suggests that an increase in pressure within the carotid sinus may be more important as a stimulus than the external pressure as suggested by others. He postulates that a hypersensitivity of the vagus nerve may exist to explain in part some of the failures to relieve the carotid sinus syndrome by surgical denervation, the vagus nerve presumably being reflexly activated by stimuli from other sensory areas in the body.

### ELECTROCARDIOGRAPHY AND ROENTGENOLOGY

The brisk disagreement regarding the validity of the Einthoven triangle hypothesis continues to flourish in medical literature. Adequate discussion of this and of other complex electrophysical problems must be left to the select few who are competent to argue in this most interesting but special field, and it will suffice here to say that Wolferth and Livezey[193] consider that the Einthoven hypothesis is subject to "enormous error," whereas Wilson and his group[194] and Goldberger[195] too, uphold the validity of the Einthoven concept. Wilson's remarks are buttressed by a wealth of technical knowledge as well as by experimental data, as is apparent to those who peruse his publications. The use of unipolar leads also is a bone of contention between these two groups, but there would appear to be little doubt that the Wilson central terminal, with which unipolar chest and limb leads can be taken, not only offers a happy solution in the choice of precordial leads but also makes available through the unipolar limb leads a new source of electrocardiographic information.

The broad range of the normal in electrocardiography has been illustrated by studies made on healthy young aviators during the recent

192. Nathanson, M. H.: Hyperactive Cardioinhibitory Carotid Sinus Reflex, Arch. Int. Med. **77**:491 (May) 1946.

193. Wolferth, C. C., and Livezey, M. M.: A Study of Methods of Making So-Called Unipolar Electrocardiograms, Am. Heart J. **27**:764, 1944.

194. Wilson, F. N.; Johnston, F. D.; Rosenbaum, F. F., and Barker, P. S.: On Einthoven's Triangle, the Theory of Unipolar Electrocardiographic Leads, and the Interpretation of the Precordial Electrocardiogram, Am. Heart J. **32**: 277, 1946.

195. Goldberger, E.: The Validity of the Einthoven Triangle Hypothesis, Am. Heart J. **29**:369, 1945.

war. Graybiel, McFarland, Gates and Webster [196] reviewed the electrocardiograms of 1,000 aviators; they noted sixteen examples of prolongation of the P-R interval beyond 0.20 second (the longest being 0.28 second) and thirty-eight examples of a QRS interval longer than 0.10 second (the longest being 0.14 second). They also describe in 1 instance a heart rate of 38. "Even after rejecting as frankly abnormal some of the extreme values observed," they state, "it is apparent that the 'normal' extends well into what has commonly been regarded as the abnormal range." Similar conclusions have been reached by Stewart and Manning [197] in an analysis of the electrocardiograms of 500 Canadian airmen. These papers call attention once again to the need for conservatism in the interpretation of borderline electrocardiographic abnormalities, particularly when clinical evidence of heart disease is lacking.

Goldberger [198] has presented a discussion of the differentiation between normal and abnormal Q waves, describing the nature and course of the spread of electrical activity over certain portions of the heart muscle which results in the appearance of Q waves in the electrocardiogram. He refers to the useful concept that the area of infarction in the myocardium acts like a window in the ventricular wall which transmits to the chest wall and the limbs the variations in potential taking place within the ventricular cavity. Both Goldberger and Myers and Oren [199] have stressed the value of the unipolar lead in the left leg in the differentiation of normal from abnormal Q waves from limb lead III. It has been demonstrated in the past by Wilson that the region of a posterior myocardial infarction usually points to the left leg; hence the unipolar lead from the left leg may show a deep or broad Q wave when this condition is present. As these authors point out, it is sometimes possible to distinguish this $Q_3$ pattern from that due to a transverse position of the heart by the findings in the unipolar leads from both the left arm and the left leg. Such a use of unipolar leads illustrates their practical clinical value.

The significance of marked left axis deviation in the electrocardiogram has been studied critically by Faulkner and Duncan,[200] who

196. Graybiel, A.; McFarland, R. A.; Gates, D. C., and Webster, F. A.: Analysis of the Electrocardiograms Obtained from One Thousand Young Healthy Aviators, Am. Heart J. **27**:524, 1944.

197. Stewart, C. B., and Manning, G. W.: A Detailed Analysis of the Electrocardiograms of Five Hundred R. C. A. F. Aircrew, Am. Heart J. **27**:502, 1944.

198. Goldberger, E.: Differentiation of Normal from Abnormal Q Waves, Am. Heart J. **30**:341, 1945.

199. Myers, G. B., and Oren, B. G.: Use of the Augmented Unipolar Left Leg Lead in the Differentiation of the Normal from Abnormal Q Wave in Standard Lead III, Am. Heart J. **29**:708, 1945.

200. Faulkner, J. M., and Duncan, C. N.: The Significance of Marked Left Axis Deviation in the Electrocardiogram, Am. J. M. Sc. **208**:205, 1944.

analyzed two hundred tracings in which $S_2$ was greater than $R_2$. Autopsy reports in 27 of the 200 cases were reviewed, as were the roentgenograms of the chest obtained in 97. These authors noted that the cardiac measurements were within the normal range in 37 per cent of those patients for whom the roentgenograms of the chest were available and that the heart was normal in 30 per cent of the autopsies. They concluded that left axis deviation of considerable degree when present in an otherwise normal tracing is to be regarded as a normal variation.

Wilson and his colleagues [201] have published a comprehensive report on the precordial electrocardiogram (recorded by means of the central terminal). In this paper the authors describe prominence of the R wave over the left side of the precordium associated with abnormal left ventricular preponderance and also refer to unusual prominence of R waves over the right side of the precordium (with relatively small R waves near the apex) in right ventricular hypertrophy. The patterns of right and left bundle branch block as illustrated by changes in the chest leads are discussed as are the abnormalities found in myocardial infarction; the writers refer to the fact that an anteroseptal infarct produces maximal abnormalities in $V_2$, $V_3$, $V_4$, whereas an anterolateral infarct is best diagnosed from leads $V_4$, $V_5$, $V_6$. They also show that posterior myocardial infarction may at times produce a depression of the S-T segments in the precordial leads, with subsequent prominence of the R and T waves, notably in leads $V_1$ and $V_2$. In a further report Wilson's group [202] has stressed the value of chest leads taken in the fourth, third and even second interspaces in locating high lateral areas of myocardial damage.

The juvenile and adult types of precordial electrocardiographic patterns have been analyzed by Battro and Mendy,[203] who found that negative or diphasic T waves in all the chest leads are common in infancy and that by the tenth year the T waves have usually become upright in leads $V_5$ and $V_6$. A similar report by Suarez and Suarez,[204] based on the precordial tracings of 161 healthy Puerto Ricans, states that a negative T wave in lead $V_1$ is normal regardless of age or sex but that negativity of the T waves in leads $V_2$ through $V_6$ is probably abnormal

201. Wilson, F. N.; Johnston, F. D.; Rosenbaum, F. F.; Erlanger, H.; Kossmann, C. E.; Hecht, H.; Cotrim, N.; de Oliveira, R. M.; Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, Am. Heart J. **27**:19, 1944.

202. Rosenbaum, F. F.; Wilson, F. N., and Johnston, F. D.: The Precordial Electrocardiogram in High Lateral Myocardial Infarction, Am. Heart J. **32**:135, 1946.

203. Battro, A., and Mendy, J. C.: Precordial Leads in Children, Arch. Int. Med. **78**:31 (July) 1946.

204. Suarez, R. M., and Suarez, R. M., Jr.: The T Wave of the Precordial Electrocardiogram at Different Age Levels, Am. Heart J. **32**:480, 1946.

in males who have reached the age of 19 although in adult females inversion of the T waves in leads $V_2$ and $V_3$ is normal.

Using dogs as their experimental animals, Bayley, LaDue and York [205] produced local ventricular ischemia and injury by temporary occlusion of a coronary artery while a continuous electrocardiographic tracing was being obtained directly from the ventricular surface. They observed an initial and extremely transient deep inversion of the T wave followed by what is usually considered to be the earliest change under such conditions, namely, elevation of the S-T segment. The authors believe, therefore, that this ischemic T wave pattern both initiates and concludes the pattern of myocardial infarction. Bayley [206] has also described an electrocardiogram taken during the illness of a 44 year old woman, whose heart at postmortem examination showed unexplained necrosis of the inner half of the wall of the left ventricle. It was notable that the electrocardiogram showed a depression of the S-T segments in leads I, II and $CF_4$, a phenomenon which Bayley characterizes as "an injury effect against the rule," which is just the reverse of what is seen with acute diffuse pericarditis. Pardee and Goldenberg,[207] in commenting on incomplete mural myocardial infarcts, have also called attention to the frequency of depression of the S-T segment and inversion of the T wave, similar to that appearing after exercise and anoxemia. This pattern is strikingly similar to the one reported by Bayley. Pardee and Goldenberg believe, however, that while these changes may be similar to those in coronary insufficiency the abnormalities are rarely found in both the limb leads and lead 4F.

The effect of stimulation of the carotid sinus, at times reenforced by an intramuscular injection of neostigmine, on the P-R interval in 16 patients with acute rheumatic fever has been studied by Gubner, Szucs and Ungerleider.[208] These workers obtained a definite prolongation of the P-R conduction time in 12 of the 16 cases; there was no significant lengthening in 16 normal controls. They determined the fact that neostigmine did not in itself prolong the P-R interval and that the effect which they had produced could be abolished by the administration of atropine. It is their suggestion that the mechanism of the auriculo-

205. Bayley, R. H.; LaDue, J. S., and York, D. J.: Electrocardiographic Changes (Local Ventricular Ischemia and Injury) Produced in the Dog by Temporary Occlusion of a Coronary Artery, Showing a New Stage in the Evolution of Myocardial Infarction, Am. Heart J. **27**:164, 1944.

206. Bayley, R. H.: The Electrocardiographic Effects of Injury at the Endocardial Surface of the Left Ventricle, Am. Heart J. **31**:677, 1946.

207. Pardee, H. E. B., and Goldenberg, M.: Electrocardiographic Features of Myocardial Infarction as Affected by Involvement of the Septum and by Complete and Incomplete Transmural Involvement, Am. Heart J. **30**:367, 1945.

208. Gubner, R.; Szucs, M., and Ungerleider, H. E.: Provocative Prolongation of the P-R Interval in Rheumatic Fever, Am. J. M. Sc. **209**:469, 1945.

ventricular block may be an inflammatory process with vascular change in the conduction system which lowers the $p_H$ in that area, interferes with tissue nutrition and thus inhibits choline esterase, allowing a potentiated vagal effect. Also working with patients with rheumatic carditis, Taran and Szilagyi [209] have elaborated on the thesis that the duration of electrical systole as measured by the Q-T interval is significantly prolonged in all cases of acute rheumatic myocarditis. Although these writers have published considerable statistical information to substantiate their belief, it remains to be seen whether this measurement will be sufficiently valid to justify its routine use. It appears that when these authors measure the Q-T interval to within 0.0001 second they convey an unjustified impression of extraordinary accuracy.

Mention should also be made of human endocardiac electrocardiography, accomplished by placing a catheter with an electrode at its tip in the chambers of the right side of the heart. Battro and Bidoggia [210] have published tracings recorded from the right auricle and ventricle which are of particular interest to those concerned with the process by which the wave of electrical activity proceeds through the myocardium during electrical systole and during the recovery phase.

Chavez, Dorbecker and Celis [211] have reproduced striking angiocardiograms which they obtained by the injection of "diodrast" through a rubber catheter inserted into the external jugular vein, and they demonstrated the undoubted clinical value of this method in the diagnosis of congenital heart disease. It is unlikely, however, that this rather formidable procedure will have more than a limited use at the present time.

### DRUGS

The pharmacologic basis of cardiac therapy is the subject of a recent paper by Gold.[212] He reviews his previous studies on digitoxin and calls attention to the rapid rate of absorption of the drug from the gastrointestinal tract and the rarity of toxic effects from the administration of a single oral digitalizing dose. He also emphasizes the occasional value of daily mercurial injections to control edema when other measures have failed.

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209. Taran, L. M., and Szilagyi, N.: The Duration of the Electrical Systole (Q-T) in Acute Rheumatic Carditis in Children, Am. Heart J. **33**:14, 1947.

210. Battro, A., and Bidoggia, H.: Endocardiac Electrocardiogram Obtained by Heart Catheterization in Man, Am. Heart J. **33**:604, 1947.

211. Chavez, I.; Dorbecker, N., and Celis, A.: Direct Intracardiac Angiocardiography—Its Diagnostic Value, Am. Heart J. **33**:560, 1947.

212. Gold, H.: Pharmacologic Basis of Cardiac Therapy (Alpha Kappa Lecture, Abridged), J. A. M. A. **132**:547 (Nov. 9) 1946.

Erickson and Fahr [213] have investigated some of the effects of lanatoside C in 39 patients with organic heart disease but without evidence of heart failure and in 14 normal controls. The drug was given by mouth, and the mechanical efficiency of the heart was subsequently estimated. These authors concluded that 87 per cent of their patients with organic heart disease showed an improved mechanical efficiency after digitalization whereas the 14 normal controls had a definite decrease in cardiac efficiency. It was their belief that digitalis exerts its action "primarily on the cardiac muscle by changing the mechanical efficiency of the heart" and that in the normal heart the drug acts as a poison.

Another view of the mode of action of the drug digoxin has been presented by McMichael and Sharpey-Schafer.[214] These English authors administered the drug intravenously and noted a lowering of both the right auricular pressure and the cardiac output in normal persons and in patients with anemia and cor pulmonale as contrasted with an increase in cardiac output in most cases of congestive failure. They believe that simple mechanical lowering of the right auricular pressure produces a similar effect and suggest that the major benefit derived from the drug may be a peripheral action on the veins, with consequent lowering of the venous pressure. In contrast to orthodox concepts, they draw attention away from the stimulating effect of the digitalis group of drugs on the myocardium itself. These writers have likewise found that simple control of rate in cases of auricular fibrillation does not produce any immediate change in cardiac output which cannot be accounted for by the accompanying fall in venous pressure. It is their suggestion that digoxin may accordingly be actually harmful when administered in cases in which high output heart failure exists, as, for example, in cor pulmonale, Paget's disease and anemia. This interesting new theory, while it may be applicable to the digitalis glycoside which McMichael and Sharpey-Schafer have studied, does not necessarily hold true for the entire group of digitalis preparations.

In an attempt to investigate further the clinical value of lanatoside C, Ray and LaDue [215] administered digitalizing doses of the drug intravenously to 62 patients with recurrent congestive heart failure who had been receiving a maintenance intake of digitalis leaf. Although

213. Erickson, E. W., and Fahr, G. E.: The Effect of Lanatoside C upon the Physiologic State of Organically Diseased Hearts Before Symptoms and Signs of Heart Failure Appear, Am. Heart J. **29**:348, 1945.

214. McMichael, J., and Sharpey-Schafer, E. P.: The Action of Intravenous Digoxin in Man, Quart. J. Med. **13**:123, 1944.

215. Ray, T., and LaDue, J. S.: The Intravenous Administration of Lanatoside C to Patients Taking Maintenance Doses of Folia Digitalis up to the Date of Hospitalization with Recurrent Congestive Heart Failure, Am. Heart J. **30**: 335, 1945.

it might have been expected that symptoms of digitalis intoxication would develop in many patients in this group, these authors report that only one such reaction occurred. Furthermore, it appeared that in 46 of the 62 cases definite clinical improvement was demonstrated. Such a study does not eliminate the necessity for caution in the administration of digitalis glycosides to patients who are known to have been receiving the drug.

The relationship of digitalis to the clotting mechanism has been the subject of a report by de Takats, Trump and Gilbert.[216] They observed 4 patients who experienced thrombotic phenomena possibly related to the use of digitalis, and, stimulated by these findings, they thereupon gave digitalis to 5 patients and determined their tolerance to heparin daily. They concluded that resistance to heparin developed as a result of digitalization and disappeared after the use of digitalis was stopped, and they reasoned that "digitalis favors the tendency to thrombosis." Employing the Lee-White method of determination of clotting time, Massie and his associates [217] also demonstrated a reduction in the clotting time in 24 patients who were receiving digitalis. These investigations may be related to the findings of Askey and Neurath,[218] who believe that because of the high incidence of fatal systemic embolism the administration of digitalis alone for congestive heart failure associated with auricular fibrillation and myocardial infarction is contraindicated. Such conclusions require further clinical study, however, as it is obvious that many of the patients who received digitalis were poor risks,

A study of changes in the plasma volume and in the body weight of normal subjects who were placed on regimens designed to promote diuresis has been described by Lyons, Jacobson and Avery.[219] Their results indicate that a reduction both in plasma volume and in body weight, with accompanying diuresis, will occur in normal persons who are placed on a moderately low salt diet with 9.0 Gm. of ammonium

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216. de Takats, G.; Trump, R. A., and Gilbert, N. C.: The Effect of Digitalis on the Clotting Mechanism, J. A. M. A. **125**:840 (July 22) 1944.

217. Massie, E.; Stillerman, H. S.; Wright, C. S., and Minnich, V.: Effect of Administration of Digitalis on Coagulability of Human Blood, Arch. Int. Med. **74**: 172 (Sept.) 1944.

218. Askey, J. M., and Neurath, O.: Is Digitalis Indicated in Myocardial Infarction? J. A. M. A. **128**:1016 (Aug. 4) 1945.

219. Lyons, R. H.; Jacobson, S. D., and Avery, N. L.: The Effect on the Plasma Volume of Dehydration Produced by a Low-Salt Diet and Ammonium Chloride, Am. Heart J. **27**:353, 1944. Lyons, R. H.; Avery, N. L., and Jacobson, S. D.: Effect of Dehydration, Produced by Mercupurin, on the Plasma Volume of Normal Persons, ibid. **28**:247, 1944. Lyons, R. H.; Jacobson, S. D., and Avery, N. L.: The Change in Plasma Volume and Body Weight in Normal Subjects After a Low Salt Diet, Ammonium Chloride, and Mercupurin, Am. J. M. Sc. **211**:460, 1946.

chloride a day or who are given this diet plus "mercupurin" (mercurophylline injection) intravenously or who receive "mercupurin" alone. They point out that a diagnosis of subclinical edema is not justified merely because diuresis and loss of weight occur with the use of these measures.

Modell [220] has compared the value of 1.0 and 2.0 cc. doses of "mercupurin" in ambulatory patients with congestive heart failure. Using loss of weight as the measure of diuresis in 37 patients, he found that two injections of 1.0 cc. semiweekly were of greater benefit than was one injection of 2.0 cc. per week and that the addition of ammonium chloride increased the amount of weight lost by about 15 per cent with both methods. He also concluded that there was no essential difference between the diuretic effect of intramuscular injection of "mercupurin" and that of intravenous injection.

The use of "mercupurin" orally has received a limited clinical evaluation by Batterman and his associates.[221] These workers have given "mercupurin" in tablet form to 81 patients in varying doses and for time intervals up to forty-nine weeks, and they have reported effective diuresis in approximately 75 per cent of their cases. Toxic reactions included albuminuria, gastrointestinal symptoms, gingivitis and elevation of the blood nonprotein nitrogen level. Although the authors consider this method of clinical value, it should be stressed that the incidence of toxicity is high in comparison with that found with administration by intramuscular and intravenous routes and also that the oral route is ordinarily of no value when the parenteral route fails. Batterman and his associates advised rest periods between courses of the drug when it is given orally.

Reports of fatalities resulting from the intravenous injection of mercurial diuretics continue to appear from time to time, although it is obvious that such disasters are rare in view of the widespread use of these preparations. Wexler and Ellis [222] have described 2 such deaths and have called attention to the fact that no sudden deaths have been reported after the intramuscular administration of a mercurial drug. Three similar fatalities have been discussed by Volini, Levitt and

220. Modell, W.: The Optimal Dose of Mercurial Diuretics, Ann. Int. Med. **20**:265, 1944.

221. Batterman, R. C.; DeGraff, A. C., and McCormack, J. E.: The Effectiveness and Safety of Mercupurin Administered Orally in Treatment of Congestive Heart Failure, J. A. M. A. **124**:1243 (April 29) 1944. Batterman, R. C.; DeGraff, A. C., and Shorr, H. M.: Further Observations on the Use of Mercupurin Administered Orally, Am. Heart J. **31**:431, 1946.

222. Wexler, J., and Ellis, L. B.: Toxic Reactions After Intravenous Injection of Mercurial Diuretics, Am. Heart J. **27**:86, 1944.

Martin,[223] who have published electrocardiograms taken soon after the injection in 2 of the cases, in both of which ventricular fibrillation was present. Waife and Pratt [224] have published the findings at autopsy on a 35 year old woman who died in uremia after receiving twenty-five mercurial injections intravenously and intramuscularly over the course of six months. Postmortem examination showed the presence of mercury nephrosis, with hemorrhagic areas in the liver, ileum and colon.

In an attempt to reduce the toxicity of mercurial preparations, Chapman and Shaffer [225] injected mercurial preparations intravenously into dogs at two or at five minute intervals; the injections were preceded by or at times accompanied with injection of ascorbic acid. Their results indicate that the lethal dose of meralluride ("mercuhydrin") for dogs was greater than the lethal dose of mercurophylline or mersalyl and theophylline. Death from the last two preparations resulted from ventricular fibrillation whereas death due to meralluride was associated with ventricular asystole. Their statistics suggest that the use of ascorbic acid prior to the injection of meralluride increases the size of the lethal dose and thus increases the margin of safety, a similar effect being obtained when ascorbic acid and meralluride are injected together. Less conclusive results were obtained when these experiments were repeated with the other two preparations. It has been suggested by Pines and his associates [226] that magnesium sulfate might also be of value in reducing the toxicity of mercurial preparations by protecting against ventricular fibrillation.

Griffith [227] has reported on the clinical use of "paredrine hydrobromide" (*p*-hydroxy-α-methylphenylethylamine hydrobromide), a drug which has several actions, including a pressor effect, slowing of the heart due to a vagus reflex and ventricular stimulation (perhaps by a lessening of the refractory period of cardiac muscle and by stimulation of the conducting tissues). He has employed this drug in heart block to

223. Volini, I. F.; Levitt, R. O., and Martin, R.: Studies on Mercurial Diuresis: V. Sudden Death Following Intravenous Injection; Report of Three Cases with Electrocardiographic Studies in Two, J. A. M. A. **128**:12 (May 5) 1945.

224. Waife, S. O., and Pratt, P. T.: Fatal Mercurial Poisoning, Following the Prolonged Administration of Mercurophylline, Arch. Int. Med. **78**:42 (July) 1946.

225. Chapman, D. W., and Shaffer, C. F.: Mercurial Diuretics: A Comparison of Acute Cardiac Toxicity in Animals and the Effect of Ascorbic Acid on Detoxification in Their Intravenous Administration, Arch. Int. Med. **79**:449 (April) 1947.

226. Pines, I.; Sanabria, A., and Arriens, R. T. H.: Mercurial Diuretics: The Addition of Magnesium Sulphate to Prevent the Toxic Effects of Their Intravenous Administration, Brit. Heart J. **6**:197, 1944.

227. Griffith, G. C.: Use of Paredrine Hydrobromide, U. S. Nav. M. Bull. **44**:284, 1945.

prevent Adams-Stokes attacks as well as in auricular and ventricular tachycardia and in auricular fibrillation and has had encouraging results. Although the physiologic and pharmacologic effects of the preparation appear to be somewhat contradictory, a further investigation of its uses is anticipated.

In conclusion, a few words are appropriate to emphasize the recent major advances in the study of cardiovascular problems. Knowledge of cardiac function in health and in disease is steadily increasing as a result of the use of new biochemical methods and the introduction of new investigative technics, notably cardiac catheterization. In particular, many cases of congenital heart disease can thus receive more adequate diagnostic study, which leads often to surgical intervention, with resultant cure or with significant clinical improvement. Dietary management of heart failure has now been recognized as of established value, and the dietary control of hypertension holds interest for the future. The availability of unlimited quantities of penicillin and streptomycin has permitted a profound drop in the mortality of bacterial endocarditis. Finally, special foundations, governmental agencies and the public at large have acquired a greater realization of the need for intensive research in the field of cardiovascular diseases and are now making possible investigative projects which may further broaden our knowledge.

# News and Comment

## GENERAL NEWS

**Resolution on Nurse Anesthetists.**—At the meeting of the Southern Surgical Association which was held in Hollywood, Florida, Dec. 9, 10 and 11, 1947, the following resolution was passed unanimously by the Association:

"Although the Southern Surgical Association has been and always will be extremely interested in the advancement of all medical sciences and particularly in anesthesia, because of complete dependence on safe anesthesia for the safe performance of a sugical procedure, it, the Southern Surgical Association, heartily disapproves of the publicity given by certain newspapers and popular lay magazines to the statement sponsored by a group of anesthesiologists who are seeking to discredit the well trained nurse anesthetist and to compel surgeons to operate only if anesthetics are administered by physician-anesthetists.

"This attempt to persuade the public that there is grave danger in a surgical operation if the anesthetist is not a certified medical specialist is already decreasing the number of efficient well trained nurse anesthetists and forcing surgeons to perform recently developed complicated operations with anesthetics administered by young hospital interns or general practitioners, neither of whom have special training or experience in the administration of an anesthetic."

**Biological Photographic Association.**—The Biological Photographic Association will hold a meeting at Houston Hall, University of Pennsylvania, Philadelphia, from September 8 to 10. There is to be an interesting exhibit of prints, color transparencies and motion pictures in the field of biologic photography. Organized symposiums and demonstrations are planned.

Further information about the meeting and about the Biological Photographic Association may be secured by writing to the secretary at University Office, Magee Hospital, Pittsburgh 13, Pa.

**1949 Annual Session of the American College of Physicians.**—The American College of Physicians will conduct its thirtieth annual session in New York City from March 28 through April 1, 1949. Dr. Franklin M. Hanger Jr., of New York City, is the chairman for local arrangements and for the program of clinics and panel discussions. The president of the college, Dr. Walter W. Palmer, Director of the Public Health Research Institute of the City of New York, Inc., and Professor Emeritus, Columbia University College of Physicians and Surgeons, is in charge of the program of morning lectures and afternoon general sessions.

Secretaries of medical societies are especially asked to note these dates and, in arranging meetings for their societies, to avoid conflicts with the college meeting for obvious mutual benefits.

**Orientation Course in Allergy.**—Northwestern University Medical School, Chicago, and the American Academy of Allergy are offering an orientation course in allergy to be given during the week of Oct. 25 to 29, 1948, inclusive. The faculty includes many men of national prominence.

# Book Reviews

**Mental Mischief and Emotional Conflicts.** By William S. Sadler, M.D. Price, $6. Pp. 396. St. Louis: The C. V. Mosby Company, 1947.

Whenever a writer attempts to explain so complex a subject as the human personality, with its conflicts and its disharmonies, in a style suited to the lay reader, all too often the result is oversimplification. In thirty-four chapters Dr. Sadler discusses practically all problems which a busy psychiatrist is likely to encounter in any single month of practice. After a few chapters devoted to basic concepts of psychopathology, he separately discusses the various neuroses, character disorders and nonorganic psychoses and concludes with a chapter devoted to psychotherapy and one on "A Philosophy of Life."

The subtitle of this pretentious work is "Psychiatry and Psychology in Plain English." In spite of this warning, the reviewer was surprised to see the problem of multiple personality traits presented as manifestations of the "personality gear shift." Another cliché likely to catch the eye of the reader is "psychic indigestion." The problem of fatigue in psychasthenia is said to lie in the fact that "psychasthenes are born tired and remain so most of their lives." The reviewer was also surprised to learn that neurasthenia, while worldwide in distribution, is more prevalent in the Rocky Mountain region, "probably because of the extra strain imposed upon otherwise predisposed nerves by the dry climate, stimulating altitudes, strong winds and excessive sunshine." Were this advice to be taken seriously, I suppose that we of the central, southern and eastern states should hasten to dissuade many from the vacations contemplated in the approaching months.

Religious and occult thought is to some writers useful in explaining phenomena which baffle the scientific mind. A paragraph in the explanation of neurotic symptoms found under the heading of "Occult Deceptions" tells us that "Neurotics do actually experience the sensations and suffer the agonies which they so pathetically tell their doctor. Although they are tricked by their imaginations they are not intentionally dishonest—they are unfortunate victims of their unconscious mind." This explanation is plausible, but many will object to the comparison of the neurotic patient with the honest psychopath. "The honest psychics," says the author, "really believe they possess psychic powers just as truly as neurotics believe in the reality of their ailments."

To say the least, the explanation of telepathic phenomena is unusual. Dr. Sadler leads us to "suspect that there exists a universal spiritual intelligence—a universal mind." He then asks: "Is it too much to suspect that there may be a Universal Intelligence whose emanations radiate to everyone who is in harmony with the Divine Mind?" He concludes that "it is not hard to understand that two minds might think the same thing at the same time, just as two radio stations may receive at the same instant a message from a vessel far out at sea." The reviewer must unfortunately admit that to hold such an opinion is indeed difficult.

Dr. Sadler concludes his book with an observation that religions of modern times have been in danger of growing weak and effeminate, that what is needed is more of the spirit of the carpenter's Son and that faith and determination in the pursuit of the higher and nobler aims of life are necessary. But since persons with psychasthenia and neurasthenia, paranoia and schizophrenia, neurosis and psychosis

make up a sizable proportion of the earth's population, the reviewer is at a loss to know how the step from worldly to Christlike teachings can be accomplished. Dr. Sadler does not elaborate on this point.

The book has an adequate index and a representative bibliography.

**Penicillin in Syphilis.** By J. Earle Moore, M.D. Price, $5. Pp. 332, with 57 illustrations. Springfield, Ill.: Charles C Thomas, 1947.

Dr. Moore was one of the first in this country to develop a clinic in which syphilis was dealt with as a branch of general medicine and to correlate his work with those ancillary laboratories for experimental study which are so effective in promoting sound practice in their vicinity. As his long and extensive clinical experience developed, it was inevitable that a book should appear from his pen and "Modern Treatment of Syphilis," previously reviewed in these columns, has been everywhere recognized as a landmark in the literature of the disease. During the war, through the Subcommittee on Venereal Disease of the National Research Council, Moore was one of the leaders in correlating civilian and military efforts to control and treat syphilis, and finally, as chairman of the Penicillin Study Panel, he has woven together the threads of knowledge which converge from clinics over the country in which the new antibiotics have been tested under his supervision. No one is better fitted, therefore, to bring out the first monograph on penicillin in syphilis, and the reader will not be disappointed. The subject is gone into with great thoroughness, beginning with sections on chemistry, pharmacology, toxicity and the action of penicillin in experimental syphilis and a discussion on the mechanism of action of penicillin. Early, latent and other types of syphilis are then taken up in detail. The whole thing is a living story of what has already been accomplished and what is now being done, with emphasis throughout on the limitations of the data so far available, the necessarily tentative character of the conclusions and the inevitability of changes, in the future, in present programs of treatment.

The book is written in Dr. Moore's simple and lucid but entertaining style. There are numerous tables, charts and illustrations. The literature is fully reviewed. In short, this monograph is definitive to date and must be the basis of departure for all future studies on the subject.

**Gynecology, with a Section on Female Urology.** By Lawrence R. Wharton, M.D. Second edition. Price, $10. Pp. 1,027, with 479 illustrations. Philadelphia and London: W. B. Saunders Company, 1947.

The second edition of this combined textbook has been brought up to date in the ever changing fields of endocrinology and therapeutics. Recent advances in both fields as applied to women are well outlined. The advances made in the detection and treatment of genital cancer are current and thoroughly discussed.

In general, as a textbook for students in the field of gynecology, the author has arranged and presented his subject matter in a clear and, for a textbook, enjoyable fashion, with documentation of disputed points and an undogmatic attitude. The section on menstruation and related phenomena is especially clear and understandable from a student's point of view. Operative gynecology has not been emphasized at the expense of office treatment, but the procedures advocated have been clearly stated both in the text and pictorially. The section on female urology emphasizes the close relationship of the latter to gynecology, a fact too often overlooked. Certainly, the gynecologist must be familiar with urologic principles in dealing with many conditions in which the specialties overlap.

In a few instances omissions are noted. For instance, in the treatment of functional uterine bleeding, the use of the male hormone is encouraged, whereas control of the condition with progesterone or with combined estrogen and progesterone therapy is mentioned in passing. The latter is more physiologic and certainly more widely used. Again, the book makes little or no mention of the adrenal hormones as related to gynecology. When discussing subtotal hysterectomy versus total hysterectomy, the author advocates the widespread use of the former, in contrast to the growing tendency in favor of the latter. Although it is true that cases should be individualized and that more skill is required for the total procedure, the reviewer believes that it should be encouraged as a means of prophylaxis against cervical carcinoma.

In spite of a few differences of opinion, this second edition is a welcome addition to the literature and should be especially useful to undergraduate students.

**Principles and Practice of Medicine.** By Henry A. Christian, M.D. Sixteenth edition. Price, $10. New York: D. Appleton-Century Company, Inc., 1947.

Although the familiar format is maintained, one notes that Osler's name no longer appears on the back strip of this sixteenth edition of the famous textbook. The Osler tradition is, however, preserved in an essay by Dr. James G. Carr dealing with the progressive changes in the book from the first edition in 1892 through those compiled by McCrae and by Christian up to the present time.

No one could be better fitted to take over the important burden of preparing a textbook than Dr. Christian. He has thoroughly revised and brought up to date all the material in a precise and scholarly way. Space forbids detailed analysis. It may be said, however, that the general method of arrangement and classification used in recent editions is continued. Some of Osler's original descriptions still remain and indeed cannot be surpassed, although such phrases as "among women, anemic, dyspeptic servant girls seem very prone (to peptic ulcer)" are perhaps a bit archaic in this day when servants no longer exist. There is always the question of allocation of space to various subjects. The reviewer still maintains, as he did in regard to a former edition, that thirty pages need no longer be devoted to typhoid fever nowadays when the disease is rarely seen, and that some of this space could be used to discuss other infections such as virus diseases, which are all dealt with in about seventy-five pages, of which only fourteen are assigned to the important group of encephalitides including poliomyelitis. On the other hand, there is practically nothing in the domain of internal medicine which is not at least touched on, and the book remains invaluable for student, physician and teacher.

**Leprosy.** By Sir Leonard Rogers and Ernest Muir. Third edition. Price, $7. Pp. 280. Baltimore: Williams & Wilkins Company, 1946.

In this book a three thousand year old subject is effectively handled by two competent authors who have had extensive experience with the material in the Orient and elsewhere. The book proper is divided into six sections: history and distribution, epidemiology and communicability, prophylaxis, etiology, clinical observations and treatment. These sections are followed by appendixes containing eighty-eight photographs. The material is well organized, with an index and bibliography.

The history of the disease is recognized as being inseparable from the clinical aspect and is infiltrated throughout the book, forming the background on which our sparse scientific knowledge of this disease is presented. Along with the history is the presentation of the public health attitudes, both ancient and modern.

The section on treatment is up-to-date (including a consideration of calcium, penicillin and streptomycin). The current drugs are considered concisely and in the light of the authors' extensive experience.

The book is readable and does not bog down with details. It gives a comprehensive and clear picture, leaving minutiae for the research worker to supply in other books.

**Tumores y seudotumores de la mama.** By Dr. Jacinto Moreno. Price, $8. Pp. 142. Buenos Aires: Lopez & Etchegoyen, S. R. L., 1946.

This book is a study on the experimental investigation of mammary tumors, in which special consideration is given to their objective anatomic pathology and clinical diagnosis. The author starts his discussion with a classification of the mammary tumors. Each pathologic entity is individually presented, and representative photomicrographs, with excellent descriptions, are included in the discussions. Emphasis is given to the management and endocrine therapy of functional mastopathy.

The treatment of mammary cancer is extensively discussed by the author. He presents a statistical review, trying to estimate his skepticism on the surgical treatment of mammary neoplasms, in which it appears that the unsatisfactory results from this form of treatment are too strongly emphasized.

A discussion is included on the prophylactic treatment of carcinoma of the breast, based on the restoration of hormonal balance with the use of thyroid, insulin and ovarian extracts according to the author's experience.

**Intracranial Complications of Ear, Nose and Throat Infections.** By Hans Brunner, M.D. Price, $6.75. Pp. 444. Chicago: Year Book Publishers, Inc., 1946.

Brunner has assembled his experiences with intracranial infections encountered in otorhinologic practice in Vienna and Chicago during the last quarter century. The monograph is written for the otorhinologist and neurologist and will be of primary interest to the former. The major intracranial complications of infections of the ear, nose and throat are thoroughly discussed, with emphasis on genesis, symptomatology and treatment. The book appears to have been hastily composed. Many chapters lack coherence, unity and clarity but not verbosity. Grammatical errors frequently distract the reader's interest and attention. Dr. Brunner is an eminent authority in otolaryngology, and the book contains a wealth of valuable material; nevertheless, the presentation is impaired by a deficiency in correct English grammar.

**Techniques and Procedures of Anesthesia.** By John Adriani, M.D. Price, $6. Pp. 418. Springfield, Ill.: Charles C Thomas, 1947.

This text is written in tabular fashion, which makes it an excellent ready reference for the busy practitioner who occasionally has to administer an anesthetic. This style of presentation makes the contents rather too rigid and with too much emphasis on trivia for use by students. Specialists in anesthesiology will object to many dogmatic statements, which would undoubtedly have been qualified were the book written in ordinary running prose form.

An introductory chapter on the nature of anesthesia and its manifestations could well have been included. This could have been in the usual literary style to good advantage. As the book now stands, the emphasis is on technics rather than on the more important physiologic considerations.

**Fundamentals of Clinical Neurology.** By H. Houston Merritt, M.D.; Fred A. Putnam, M.D., PH.D., and Tracy Jackson Putnam, M.D. Price, $6. Pp. 289, with 96 illustrations. Philadelphia: The Blakiston Company, 1947.

This excellent book represents an effort to give a thorough discussion of neurologic diagnoses without entering the domain of controversial or esoteric neuroanatomy or physiology. While it follows in general plans which have previously been used by others, there are a number of outstanding features: fine paper and good type, numerous reproductions of anatomic preparations, lucid diagrams of nervous pathways and centers, practical clinical diagnostic tables and photographs of patients with various clinical lesions. The reviewer believes that this book fulfils very well the authors' purpose of aiding the general physician in the fundamentals of clinical neurology.

**Clinical Hematology.** By Maxwell M. Wintrobe, M.D., PH.D. Second edition. Price, $11. Pp. 862, with 197 illustrations and 14 plates, 10 in color. Philadelphia: Lea & Febiger, 1946.

This revision of Dr. Wintrobe's excellent treatise brings the subject of hematology fully up to date. However, the greatest feature of the book is its really comprehensive handling of the subject. The introductory chapters on the blood and the blood cells are obviously from the pen of an authority who has done original work in the field. The discussions of disease are satisfying and deal in a critical way with the many intriguing problems of pathogenesis. There are innumerable excellent drawings and charts, and each chapter is followed by a really full bibliography. It is a comparable work from the standpoint of thoroughness and scholarship.

**Pharmakologie als theoretische Grundlage einer rationellen Pharmakotherapie.** By K. O. Moller. Price, 48 Swiss francs. Basel: Benno Schwabe & Co., 1947.

It is stimulating to find such an extremely satisfactory book coming out of war-torn Europe. The author is obviously an accomplished scholar and thoroughly familiar with his subject in an authoritative way. His idea has been to bridge the gap between pharmacology and clinical medicine. To effect this end, he discusses first the chemistry and pharmacology of various substances and then describes the clinical applications. Innumerable preparations are taken up, so that the book really becomes a small encyclopedia. The information given is up up-to-date and in line with sound practice. The book is well printed on good paper and is not paralleled by any English work as far as is known. It is to be highly recommended.

**Diagnostic electrocardiographique.** By André Jouve, Jacques Senez and Jean Pierron. Price, 860 francs. Pp. 364, with 217 illustrations. Paris: Masson & Cie, 1946.

This monograph is essentially of the usual type. The material is presented without too much attention to the mechanisms for the various electrocardiographic complexes encountered in normal and diseased states. The illustrations are fairly good. Some of the more recent publications on electrocardiography have not been included, an omission most probably due to the war. This monograph is not to be particularly recommended except as a source of information for those who are curious about the manner in which electrocardiography is practiced and taught in France.

**Annual Review of Physiology.** Volume IX. Price, $6. Pp. 736. Stanford University, Calif.: Annual Reviews, Inc., 1947.

The ARCHIVES saluted this important book shortly after the first volume had appeared. Subsequently, the second, third and fourth volumes were received with the same enthusiasm that greeted the first.

The ninth volume is like its predecessors and lives up to their standards. The "Annual Review of Physiology" is intelligently compiled; it is written by a carefully selected list of contributors and each chapter concludes with an admirable list of bibliographic references. Each supplement continues to make the series an indispensable tool for those interested in internal medicine and its advances.

**The Compleat Pediatrician.** By Wilburt C. Davison, M.D. Fifth edition. Price, $4. Durham, N. C.: Duke University Press, 1946.

Revised and rewritten to include newer advances in pediatrics, the fifth edition of this book presents a concise, up-to-date digest, combining in one volume the practical pediatric facts usually found in several. Used for the purpose intended, it should be of invaluable aid to any physician who deals with infants and children. It is recommended most highly to student and practitioner alike.

**Principles and Practice of Tropical Medicine.** By L. Everard Napier. Price, $11. Pp. 917. New York: The Macmillan Company, 1946.

The events of World War II brought tropical medicine into sharp focus and stimulated the appearance of numerous articles and several books on the subject. The author of this volume, like previous authors, also has had difficulty in deciding what diseases to include under the title of "tropical diseases." Thus one observes the omission of the most prevalent one, tuberculosis, and others of importance, such as typhoid and tetanus, but finds the inclusion of tularemia, which the author states is caused by Brucella (sic!) tularensis, seven day fever of Japan, Rocky Mountain spotted fever, Weil's disease, trichinosis and the tapeworm infection due to Diphyllobothrium latum—all nontropical diseases.

There are a number of misleading statements, such as the statement that undulant fever occurs in the southern states of the United States of America, with no reference to its greater frequency in the North Central States, and, with reference to coccidiosis, that a heavy infection "will cause a catarrhal condition of the mucosa rather than ulceration and will interfere with its (small intestine?) functions." The statement that Iceland is an important focus of hydatid disease has not been true for forty years, and this should be known generally.

The author evidently has had little access to the literature on the results of observations made during the war. For example, most of the recent work concerning typhus and its dramatic control in Italy and elsewhere is not referred to, nor is there any reference to the work done by the United States Army and Navy with reference to filariasis. It is in the section dealing with malaria that the most obvious omissions and lack of recent information are revealed. Some of the most obvious errors may be indicated as follows: 1. Pamaquine naphthoate is said to enhance the action of quinine and quinacrine hydrochloride in completely eradicating a benign tertian infection and thereby preventing a relapse. 2. The dose of quinacrine hydrochloride is given as 0.1 Gm. three times a day for five days, with no reference to the demonstration that such a dose is inadequate to control attacks of malaria. 3. In a discussion of the complications in administration of quinacrine hydrochloride, no reference is made to lichen-planus-like cutaneous lesions, which

have been thoroughly studied. 4. Pyrethrum is given as the repellent of choice in India before the introduction of DDT (4,4′-dichlorodiphenyltrichloroethane), neither one of which is generally considered to be a repellent, however. The author gives oil of citronella a prominent place as a repellent and in a three line note refers to dimethylphthalate, "indalone" (butyl ester of 3,4-dihydro-2,2-dimethyl-4-oxo-1,2-pyran-6-carboxylic acid) and "612 insect repellent" (2-ethyl-1,3-hexanediol). He recommends their use in a shellac paint, a method attempted in experiments but not successful. There is, however, no discussion of these important repellents. A discussion of DDT is limited to a line or two in the following phraseology: "It seems possible that DDT eventually will replace Pyrethrum as the insecticide." These are but a few of the examples which could be cited of instances in which the author has failed to record well known recent observations which have served to advance knowledge of tropical medicine.

The author does not dwell on laboratory methods of procedure; however, he does give numerous procedures throughout the text. There are a number of prominent omissions, however, in these procedures, an example of which is the importance of the acid-ether concentration method for the detection of the ova of Schistosoma and other worms. There is no discussion of the poisonous plants of the tropics, but there is a section dealing with snakes. There are a number of illustrations in the text, many of which have been drawn from articles by other authors, but for the most part reproduction of the figures has not approached the quality of those in other texts on the subject.

In spite of these criticisms, the book does contain a considerable amount of useful information, especially that which has been gained by the author's personal experience, and if read with discretion it may prove to be of use to the clinician whose access to other texts may be difficult.

**Fosforyleringsprocessers betydning for resorption og assimilation.** By Kaj Kjerulf-Jensen. Pp. 191. Copenhagen: Arnold Busck, Nyt Nordisk Forlag, 1942.

This monograph, published in August 1942, but reaching the United States just recently, describes further studies, undoubtedly inspired by Professor Lunsgaard, which continue the brilliant work on absorption coming from the Copenhagen laboratories. As the author states, "the main purpose of the present investigations has been to demonstrate the significance of phosphorylation processes for the mechanism of active absorption of monosaccharides and amino acids and for the assimilation of monosaccharides."

The book is divided into two parts. Part I, consisting of eight chapters, reviews current opinion on the absorption of specific monosaccharides from the intestinal tract and discusses the role of various phosphorylating systems (donors and acceptors), glycogen formation, absorption by the renal tubule and the chemical nature of phosphorylated compounds participating in these reactions. The section closes with a brief discussion of the possible hormonal regulation of these processes and observations on the simultaneous absorption of glucose with galactose, glycin or fatty acid, causing a reduction in the absorption rate of glucose, which the author thinks may indicate a common absorption mechanism of these substances.

Part II, also of eight chapters, describes methods and experiments and presents data obtained. Observations are made on the pronounced decrease in inorganic phosphate, accompanied with a moderate increase in acid labile phosphate, probably adenosintriphosphate, in the intestinal mucosa during the absorption of amino acids such as glycine, alanine and glutamic acid. Phosphorylation of adenylic acid in

the intestinal mucosa "probably only takes place because amino acids are unsuitable as phosphate acceptors." The author expressed the opinion that present evidence does not justify the assumption of an intermediary phosphorylation of amino acids during absorption. He demonstrated the accumulation of fructose-1-phosphoric acid in the intestinal mucosa of rats during the absorption of fructose. Inhibition of absorption of glucose and galactose by phlorhizin poisoning (which interferes with phosphorylation) was confirmed. On the other hand, the rate of absorption of fructose was uninfluenced by phlorhizin in the rabbit and decreased about 10 per cent in the rat. The author's experiments confirmed previous observations of Robinson and Tanko that fructose-1-phosphoric acid cannot be dephosphorylated selectively, i. e., transformed into the corresponding glucosephosphoric acid, which probably accounts for the accumulations of fructose-1-phosphate within the mucosa during fructose absorption. In the final chapter, evidence is produced by the use of radioactive phosphorus to show that in the rabbit about 15 mg. of fructose can be absorbed from the intestine per minute. It forms fructose-1-phosphoric acid in the intestinal mucosa and is rapidly renewed.

The monograph has an excellent summary in English. It is also stated that a description in English of the experimental work may be found in *Acta Physiologica Scandinavica,* 1942.

**Science and Scientists in the Netherlands Indies.** Edited by Pieter Honig and Frans Verdoorn. A Review of Research and Exploration in the Netherlands Indies. Prepared Under the Auspices of the Board for the Netherlands Indies, Surinam and Curaçao. Price, $4. New York: Board for the Netherlands Indies; G. E. Stechert, 1945.

This book is worth reading. It gives an attractive account of life in the Netherlands Indies as observed through the eyes of men with scientific training. One gets an idea not only of the country but also of the people, the climate, the plant and animal life and the history that has made civilization go forward there so steadily.

There are several chapters which deal with medicine. Donath and van Veen describe the fundamental researches on beri-beri by Eijkman, who proved that vitamin $B_1$ was the important factor in the disease. There are five sections which tell the story of cultivation of quinine. An article by Otten van Stockum outlines her researches on rabies—unfortunately interrupted by her death. De Waart discusses medical education in that part of the world, stating that a medical school was opened in Batavia in 1852 and showing how since then medical education in the Netherlands East Indies has progressed satisfactorily. Perhaps the most interesting part of the volume dealing with medicine is prepared by Snapper, who summarizes much of what has been done to improve public health. Vaccination for smallpox was introduced in 1804 by keeping the vaccine alive on the way from Mauritius to Batavia through a few healthy children who were vaccinated successively on the journey; now smallpox there has been practically eradicated. Malaria has been controlled. Cholera has been made to disappear. Plague is much less serious than it was thirty years ago. Snapper's concluding words seem well taken: "The physicians of the Netherlands owe a debt of gratitude to their colleagues who have transformed the notoriously unhealthy Netherlands Indies into a healthy territory."

One of the underlying purposes of the book is to find readers who will feel drawn to the Malaysian Islands and who will offer their scientific training and knowledge for the good of mankind in that region. It is a stimulating challenge to anyone with the blood of adventurers or pioneers in his veins.

**Adolescent Sterility.** By M. F. Ashley-Montagu. Price, $3.50. Pp. 159. Springfield, Ill.: Charles C Thomas, 1946.

The author of this monograph has a gift for writing, so that he can make the commonplace unusual and any subject out of the ordinary of absorbing interest. His approach to any discussion is always the scholar's; his use of English is excellent, his way of thinking is logical and his conclusions are sharply pointed. For these reasons, if for no other, his publications are worth reading.

Many years ago he became curious about the basis for the well known anthropologic belief that women rarely produce children until several years after their onset of menstruation. Here he has assembled all the available information on this broad subject; it proves to include not only a considerable volume of experimental data but also a wealth of clinical observation.

His conclusions seem reasonable. He thinks that in the human species conception is possible at or even before the first estrus; when it occurs near the commencement of the first menstruation, however, there is generally a high infant and maternal death rate. The physical changes of puberty are normally followed, after the lapse of a variable amount of time, by ovulation. This takes place through a complicated interplay of anterior pituitary hormones, including the effect of one which acts on the ovary in such fashion as to cause an ovum to break through the ovary, to pass into the uterus and to luteinize, leaving behind its follicular investment.

In the uterus, under the influence of another anterior pituitary hormone, prolactin, the deposited ovum continues to undergo organization into a luteal body, and this secretes a hormone, progesterone, which prepares the uterus for pregnancy. It is not until prolactin is secreted and the corpus luteum produces progesterone that successful pregnancy becomes possible.

This monograph will interest clinicians who have dealings with endocrinology as well as experts in the field. It is a carefully thought out and ingeniously reasoned presentation.

**Physical Chemistry of Cells and Tissues.** By Rudolph Höber, with the collaboration of David I. Hitchcock and others. Price, $9. Pp. 676, with 70 illustrations. Philadelphia: The Blakiston Company, 1945.

This is a "renaissance" rather than a revision of Höber's earlier book in German by the same title and consists of separate sections by various authors, covering certain aspects of physical chemistry and physiology. The title emphasizes the former because of the conviction of the authors that "it is not only possible but of importance to anchor physiology even deeper in physical chemistry than was done previously."

The subject matter is arranged systematically from the standpoint of complexity. The first two sections comprise a survey of classic physical chemistry—selected topics in physical chemistry by David I. Hitchcock and properties of large molecules by J. B. Bateman. The subsequent six sections deal with the physiology of cells and tissue—permeability of cells and properties of cell membranes by Rudolf Höber; influence of ions and narcotics on cell activity (Höber); respiration of cells and tissues by David R. Goddard; contractility of muscle by Wallace O. Fenn, and passive penetration and active transfer in animal and plant tissues (Höber). The topics discussed, too numerous to be listed here, include the formation of urine, gastric juice and saliva, intestinal absorption, respiratory enzymes and many others of interest to those engaged in medical research.

In general, the book is the embodiment of a point of view rather than a comprehensive treatise on physiology. It is of particular interest in providing a different approach than the majority of texts on the subject, in giving the physicochemical background of many of the concepts of physiology and in including data on a great variety of species. The individual sections are clearly organized and well written, and they provide excellent surveys for the scientifically trained general reader. For the material covered, the book is a valuable source of reference, with good author and subject indexes, almost two thousand references to the literature (through 1943) and general biliographies in connection with each section.

**Estudio crítico del tratamiento médico de la insuficiencia cardíaca.** By Blas Moia, M.D. Pp. 107. Buenos Aires: El Ateneo, 1945.

This work has been written with the purpose of sharply defining the indications for and actions of the therapeutic recourses of undisputed value in the treatment of congestive heart failure. The study has been made bearing constantly in mind the modern concepts of cardiac pathologic physiology which by enlarging fundamentally the knowledge of the mechanism of heart failure have narrowed the limits to which the therapeutic scheme must be adjusted. Presented in conjunction with the author's basic material are abundant and extensive references to European and American investigators.

The monograph's introductory chapter logically consists of a comprehensive and explicit discussion on the pathologic physiology of congestive heart failure. Having presented these fundamentals, the author proceeds in the second chapter to discuss the use of digitalis compounds in cardiac insufficiency. The literature on the subject is thoroughly reviewed, and a critical study is presented, based on the author's own observations. The final chapter is an evaluation of therapeutic measures of common use in the treatment of cardiac failure, most of which are designed to diminish directly or indirectly blood stasis and its effects. In succession, the author discusses the problems of diet, choice and use of diuretics, indications for and technic of phlebotomy, laxatives, physical and mental rest, sedation, uses of hypertonic glucose solutions and oxygen therapy. These measures being of basic importance in the management of congestive failure, the author lays particular stress on their significance, emphasizing their consideration in the medical regimen of the pregnant patient with cardiac disease.

The physiologic approach considerably enhances the effectiveness of the presentation of this critical study. For the reader interested in a further exploration of the literature on the subject there is listed an extensive bibliography.